Development of Gold-Catalysed Reactions and C-H Functionalisations

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Abstracts

This thesis is comprised of an introductory chapter, followed by four chapters outlining the research undertaken by the author throughout the duration of study.

Chapter 1 provides an introduction to homogeneous gold(I) catalysis, focusing on the selective hydrofunctionalisation of 1,3-disubstituted allenes and in particular axial-to-point chirality transfer.

Chapter 2 describes the development of the first gold-catalysed intermolecular hydroalkoxylation of 1,3-disubstituted allenes to occur with excellent chirality transfer. The substrate scope and limitations of the reaction were investigated. A wide range of allenes and alcohols were shown to be suited to the reaction, with excellent chirality transfer achieved through prevention of the competing allene racemisation.

Chapter 3 outlines the successful development of gold-catalysed hydroarylations of 1,3-disubstituted allenes. Excellent chirality transfer for the hydroarylation of allenes was achieved for the first time and the scope was extended to nucleophiles previously reported to be unsuited to the hydrofunctionalisation of 1,3-disubstituted allenes.

Chapter 4 presents the first dual gold and photoredox catalysed aryl-aryl cross coupling which occurs through C-H activation. This work also constitutes the first gold-catalysed C(sp^2)-H activation reaction which does not require stoichiometric oxidant.

Chapter 5 details the development of a metal-, light- and photocatalyst free Minisci-type alkylation procedure which is suitable for the late-stage C-H functionalisation of *N*-heteroarene and 1,4-quinone moieties, and uses cheap and readily available carboxylic acids.

Acknowledgements

I would like to thank Ai-Lan for the opportunity to do my PhD in the Lee group and for all her expert support, guidance and encouragement throughout my PhD. I could not have asked for a better supervisor and will always be grateful for Ai-Lan's amazingly constant enthusiasm and optimism.

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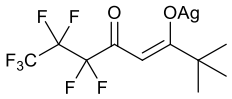
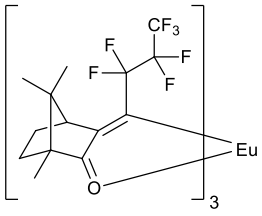
My most important personal thank you is to Claire Lamb who has made my PhD much easier through her constant advice, support and friendship as well as bizarre and inappropriate conversations, poems and balloons with exactly the correct number of 'do's.

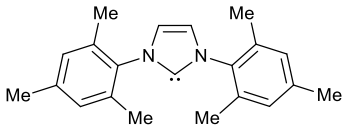
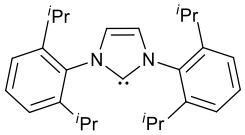
Table of Contents

Abbreviations

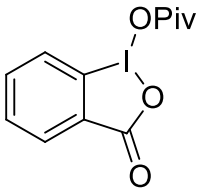
<	Less than
>	Greater than
α	Alfa
Å	Ångström (1 x 10^{-10} m)
β	Beta
δ	NMR Chemical shift (ppm)
γ	Gamma
°C	Degrees Celsius
Ac	Acetyl
Ag(FOD)	(2,2-Dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedionato)silver(I) 
Ar	Aryl group
Boc	*tert*-Butyloxycarbonyl protecting group
Bn	Benzyl
bpy	2,2'-Bipyridine
^{t}Bu	*tert*-Butyl

Bz	Benzoyl
CFL	Compact fluorescent lamp
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
dF(CF_3)ppy	2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine
DFT	Density functional theory
DIAD	Diisopropyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
DMF	Dimethyl formamide
DMSO	Dimethylsulfoxide
d.r.	Diastereoselective ratio
dtbbpy	4,4'-di-tert-butyl-2,2'-bipyridine

Cbz	Carboxybenzyl
CSP	Chiral Stationary Phase
conc.	Concentration
e.e.	Enantiomeric Excess
e.r.	Enantiomeric ratio
EI	Electron ionisation
ESI	Electronspray ionisation
equiv.	Equivalent
Et	Ethyl
EtOAc	Ethyl Acetate
$Eu(hfc)_3$	Europium *tris*[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] 
g	Gram(s)
h	Hour(s)
HAT	Hydrogen atom transfer
Het	Heteroarene

HOMO	Highest occupied molecular orbital
HRMS	High resolution mass spectrometry
Hz	Hertz
IMes	1,3-dimesityl-1,3-dihydro-2H-imidazol-2-ylidene 
IPr	1,3-*Bis*(2,6-diisopropylphenyl)imidazol-2-ylidene 
IR	Infra-red
J	Coupling Constant
LED	Light emitting diode
LUMO	Lowest unoccupied molecular orbital
Me	Methyl
MeCN	Acetonitrile
MHz	Mega Hertz
min	Minutes

mg	Milligram(s)
mL	Millilitre(s)
mmol	Millimole(s)
mol	Mole(s)
mol. sieves	Molecular sieves
M	Molar (mol L^{-1})
Mp	Melting point
Ms	Methanesulfonyl (Mesyl) protecting group
NBSH	2-Nitrobenzenesulfonylhydrazide
NHC	N-Heterocyclic Carbene
NMR	Nuclear magnetic resonance
NTf_2	*Bis*(trifluoromethanesulfonyl)amide
Nu	Nucleophile
OTf	Trifluoromethanesulfonate (Triflate)
OTs	*p*-Toluenesulfonate (Tosylate)
p	Para
PBX	1-Pivaloyloxy-1,2-benziodoxol-3(1H)-one



Piv	Pivaloyl
Ph	Phenyl
ppm	Parts per million
Ph_3P	Triphenylphosphine
^{i}Pr	Isopropyl
R_f	Retention Factor
r.t.	Room Temperature
Selectfluor	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
TBAI	Tetrabutylammonium iodide
Temp.	Temperature
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TLC	Thin Layer Chromatography

Tol	Tolyl
Ts	Toluenesulfonyl (tosyl)
XPhos	2-Dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl

Chapter 1: Introduction

1.1 A brief introduction to gold

1.1.1 Metallic gold and its uses

Gold is probably one of the most well-known and obsessed over elements in the periodic table, with almost everyone having heard of it. It is one of relatively few elements found in its elemental form and has been used for centuries as currency, as well as in artwork and jewellery. These uses depend on gold's inert nature which is possibly best demonstrated by the many ancient gold artefacts which have long outlived the civilisations which created them. This inert nature also means that metallic gold is non-toxic and causes no allergic reaction in our bodies, allowing its extensive use in dentistry.[1] Also drawing on these properties, gold nanoparticles have been shown to have biomedical applications in both drug delivery and imaging.[2-5] It is perhaps this apparent non-reactivity that led chemists to previously overlook gold as a catalyst.[1] However, interest in the area has picked up since the turn of the millennium, and the field of homogenous gold catalysis is now being heavily investigated.[1, 6-11] Gold's unique reactivity and selectivity is quickly establishing it as an important contributor to the field of metal catalysis as a whole.

1.1.2 Electronic properties of gold

Gold's reactivity, as with any element, is governed by its atomic structure. However, gold's electronic properties offer some particularly unusual and interesting characteristics due to the relativistic effect.[10] This effect can dictate how atoms bind and react and so is important for understanding gold's reactivity.[12] The relativistic effect comes into play in heavier atoms when the speed of the electrons in the s and p orbitals is close enough to the speed of light that their mass becomes significant. As the effective mass of these electrons increases, the radius of the s and p orbitals decreases and this reduction in radius provides more shielding of the d and f orbitals. In gold's valence orbitals, this translates to a shift in orbital energies with the 6s orbital being lowered in energy and the 5d orbital increasing in energy. The spin-orbital coupling also causes a splitting of the 5d orbitals (**Error! Reference source not found.**.[10]

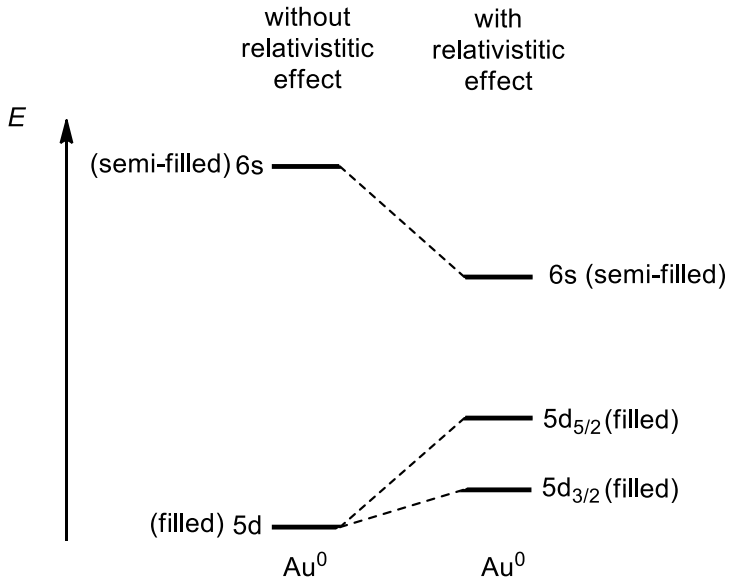


Figure 1.1: Hypothetical change in orbital energies before and after considering the relativistic effect[12]

Since gold has a valence electron configuration of $5d^{10}6s^{1}$, the stabilising of the 6s orbital gives gold a high ionization potential and high electron affinity. This makes gold one of the most electronegative metals in the periodic table.[12] Also, because the 6s orbital is stabilised and the 5d orbital destabilised, the orbitals are closer in energy, leading to s-d hybridisation. This gives gold some covalent bonding character and also gold's famously alluring colour, all due to the relativistic effect.[12, 13]

When bound, gold predominantly exists in Au(I) and Au(III) oxidation states.[12] Au(III) species are commonly found as 4-coordinate 16-electron species, similar to Pt(II) complexes. However, Au(I) complexes, more unusually for transition metals, are generally linear, 2-coordinate 14-electron complexes.[12] This gives rise to catalytically active $LAu(I)^{+}$ species with a diffuse bonding orbital which can act as a soft Lewis acid. $LAu(I)^{+}$ species are particularly good at coordinating to and so activating carbon-carbon multiple bonds such as alkynes, alkenes and allenes. The π-electrons of the multiple carbon-carbon bonds are in diffuse orbitals and are therefore readily coordinated by the soft Lewis acid $LAu(I)^{+}$ species. For this reason the Au(I) catalysts are often said to be carbophilic and are referred to as π-acids.[7] Au(III) catalysts, while also able to activate multiple carbon-carbon bonds, tend to be more oxophilic than Au(I) and will coordinate more readily to harder groups. Au(I) catalysts are therefore more

commonly employed for activating carbon-carbon multiple bonds due to their better selectivity.

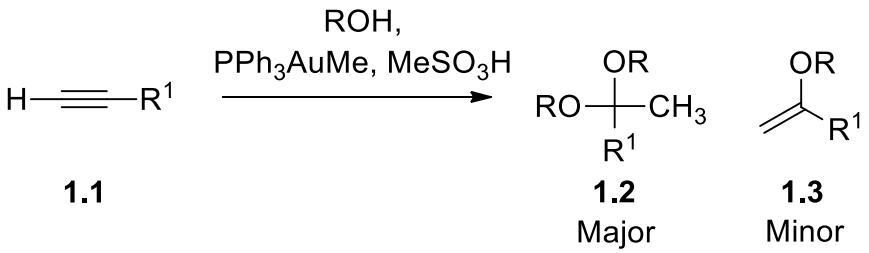
Another consideration to take from the electronic structure of gold, which has an effect on its action as a catalyst, is the full and diffuse 5d orbital. Since the 5d electrons in this diffuse orbital incur less electron-electron repulsion, they are more tightly held, which leads to oxidative addition being disfavoured.[10, 12] This resistance to oxidation means Au(I) catalysts can be exposed to oxygen, allowing air and moisture stable catalysts to be developed.[10] It should be noted that although gold is resistant to oxidation under air, the redox cycle can be easily accessed using more powerful oxidants. In recent years a range of cross-coupling reactions exploiting the Au(I)/Au(III) redox cycle of gold have been developed.[14] This area has been greatly expanded through the use of photoredox catalysis[15] and is discussed in more detail in Chapter 4.

1.2 Introduction to gold catalysis

The field of gold catalysis, despite only having been heavily investigated since the turn of the millennium, is now very broad and great progress has been made in both heterogeneous[16] and homogeneous catalysis.[1] Heterogeneous catalysis has received a large amount of attention due to its potential application to industrial processes.[17, 18] However, a much richer range of transformations can be achieved through homogeneous gold catalysis.[1] Since the field of homogeneous catalysis is so expansive, the following introduction gives only a taste of the types of reactions which can be carried out. Concentrating on carbon-carbon multiple bond activation, this introduction to homogeneous gold catalysis will first give some examples of gold-catalysed reactions with alkynes and then focus on gold catalysis with allenes, which is the main subject of the Chapters 2 and 3 of this thesis. C-H activation using gold catalysis represents another important field which is relevant to this thesis and is introduced as part of Chapter 4.

1.2.1 Homogeneous gold catalysis with alkynes

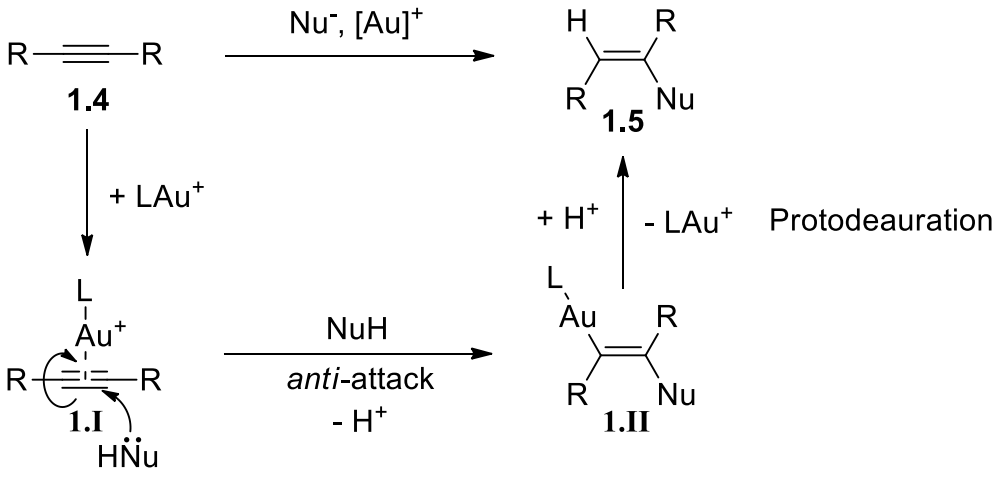
One of the first gold(I)-catalysed reactions, reported by Teles *et al*., was the addition of alcohols to terminal alkynes (**1.1**).[19] PPh_3AuMe, in the presence of $MeSO_3H$, was used to catalyse the hydroalkoxylation of alkynes and the major product formed (**1.2**) was the result of double addition to alkyne **1.1** (Scheme 1.1).



Scheme 1.1: Early example of addition of alcohol to alkynes[19]

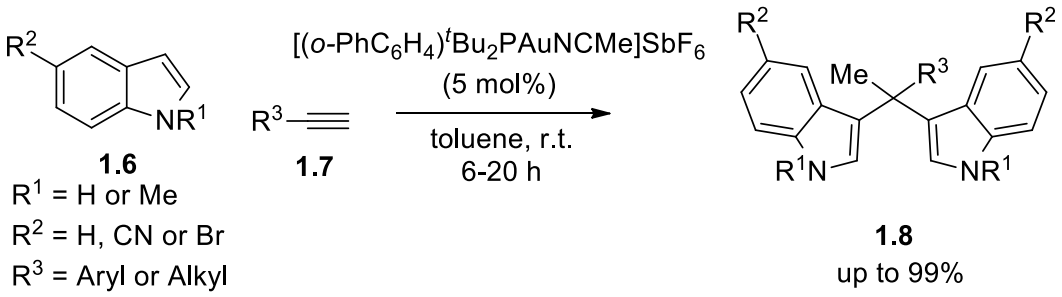
Some more modern reaction conditions can be found in a review by Goodwin *et al.*[20] along with a discussion of the regioselectivity issues with non-terminal alkynes and reactions with water as the nucleophile.

The hydroalkoxylation of alkynes generally proceed *via* the mechanism shown in Scheme 1.2. The gold catalyst first coordinates to the C-C bond of alkyne **1.4** then the nucleophile attacks *anti* to the gold (**1.I**) and finally product **1.5** is obtained by protodeauration of intermediate **1.II** (Scheme 1.2).



Scheme 1.2: General mechanism for C-C bond activation and nucleophilic attack

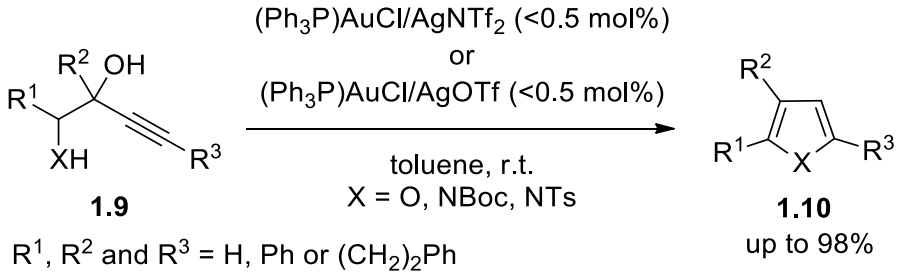
Since the initial work by Teles *et al.* (Scheme 1.2), a range of different nucleophiles have been added to alkynes *via* this general mechanism (Scheme 1.2).[1] The most heavily investigated of these hydrofunctionalisations include hydroamination and hydroarylation.[1] An example of the latter is shown below (Scheme 1.3) with double addition of the indole being obtained as the product (**1.8**). Pleasingly, pyrroles were also used successfully as nucleophiles under Echavarren's conditions (Scheme 1.3).[21]



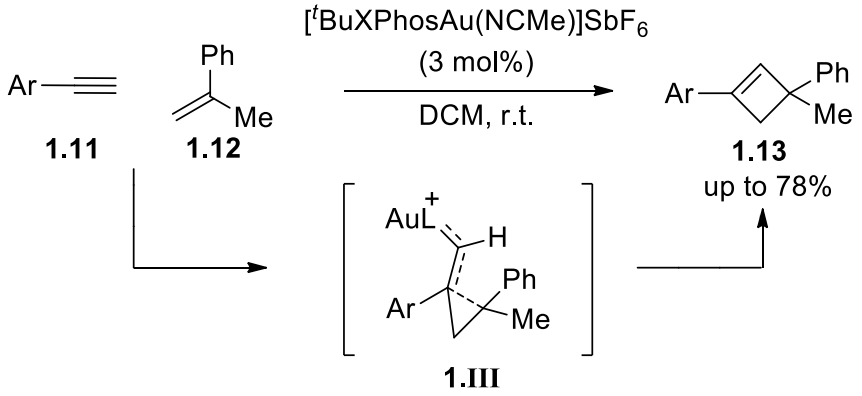
Scheme 1.3: Hydroarylation of alkynes[21]

Single addition can now also be achieved in some cases, as discussed in detail by Hashmi in his recent report[22] and the intramolecular hydroarylation variation of this reaction was also successfully reported by Echavarren[21] and others.[1]

Intramolecular hydrofunctionalisations with heteroatoms can also be performed to give heterocyclic products.[23-25] The high yielding example in Scheme 1.4 proceeds with low catalyst loading through a 5-*endo* cyclisation and dehydration to give the substituted furan and Boc or tosyl protected pyrrole products **1.10**.



Scheme 1.4: Gold(I)-catalysed synthesis of substituted furan and pyrroles[23]



Scheme 1.5: Gold(I)-catalysed [2 + 2] cycloaddition of alkynes and alkenes[26]

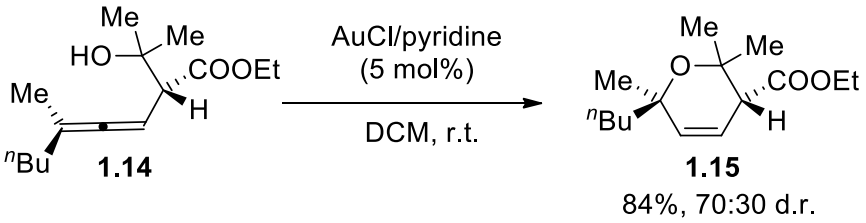
Besides hydrofunctionalisations, cycloadditions of alkynes can also be catalysed by gold (Scheme 1.5) proceeding *via* selective activation of the alkyne (**1.11**) by Au(I), followed by alkene (**1.12**) attack to give the cyclopropyl gold(I) carbene intermediate **1.III**. Intermediate **1.III** is subsequently converted through to the product (**1.13**) in good yield.[26] The intramolecular version of this reaction can also be carried out and proceeds through a similar intermediate to give often bicyclic products, albeit through more complicated mechanisms.[27, 28]

The examples given above highlight some of the main types of reactivity which occur in alkynes and give a good indication of the types of reactions which can be achieved with allenes as substrates.

1.3 Homogeneous gold catalysis with allenes

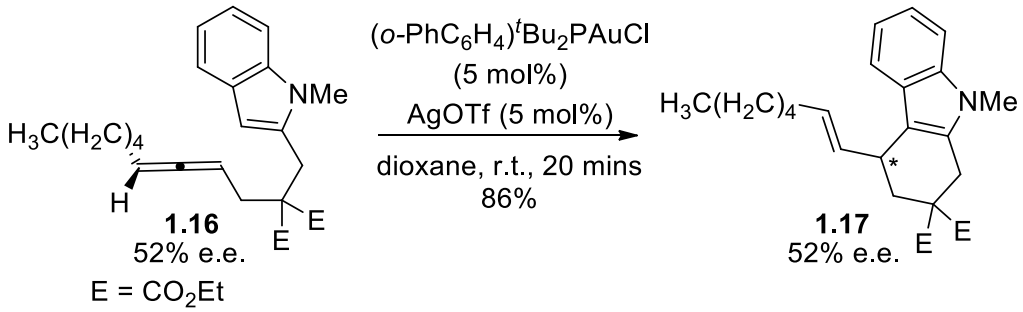
1.3.1 Intramolecular gold catalysis with allenes

Some of the first examples of hydrofunctionalisations of allenes were intramolecular heteroatom additions, giving rise to heterocyclic products. In the following selective example (Scheme 1.6**Scheme**), the allene (**1.14**) is activated by the gold(I) catalyst and subsequent nucleophilic attack by the hydroxyl group produces the dihydropyran product (**1.15**), after deprotonation of the oxygen and protodeauration.[29]



Scheme 1.6: Gold(I)-catalysed intramolecular hydroalkoxylation of an allene[29]

As well as many examples of intramolecular hydroalkoxylations,[1, 30, 31] similar intramolecular gold-catalysed reactions have been reported with heteroatoms other than oxygen, such as nitrogen[1, 30, 32] and sulphur.[1] Intramolecular hydroarylations (Scheme 1.7) have also been reported and as with intramolecular hydroalkoxylations (Scheme 1.6), they have been shown to proceed with excellent chirality transfer.[30, 33]



Scheme 1.7: Intramolecular hydroarylations with chirality transfer[30]

Intramolecular hydrofunctionalisation reactions of types discussed above can give products with various ring sizes and can occur through both *exo* and *endo* ring closures. Being intramolecular, constraints on the ring size help to give some control over which position of the allene is attacked and so excellent selectivity can be

achieved. In enantioenriched substrates, chirality transfer is also achieved through the intramolecular nature of the mechanism. For example, in Scheme 1.6, the hydroxyl group can only attack from the upper face of the allene in substrate **1.14**, thereby favouring the formation of one diastereomer of the product **1.15**. Furthermore, cyclisation to give the 6-membered ring is much less sterically demanding than reaction at the other end of the allene, which would give a strained 4-membered ring. This control of the products obtained is lost when we look at intermolecular addition of nucleophiles to allenes. However, there are still many examples which show excellent selectivity and these examples will be discussed later in Section 1.3.5. Before these intermolecular examples are discussed, the following section has been included to better explain and define the selectivity issues faced in intermolecular hydrofunctionalisations.

1.3.2 Selectivity issues in intermolecular hydrofunctionalisations of allenes

As discussed, the early examples of selective hydrofunctionalisation of allenes were intramolecular. This is perhaps due to the large number of selectivity issues associated with the intermolecular variant.

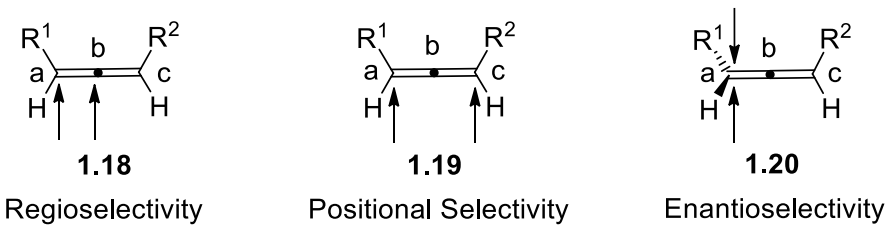


Figure 1.2: Selectivity issues in intermolecular allene reactions

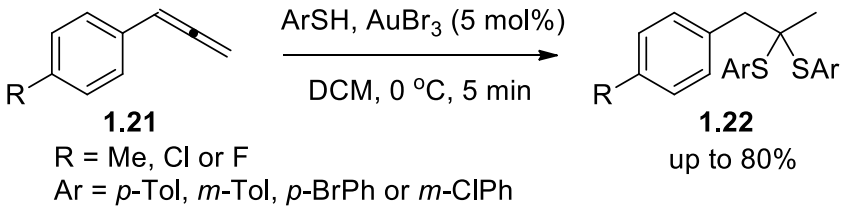
Stereoselectivity, chemoselectivity and regioselectivity are all potential issues in both allene and alkyne hydrofunctionalisations. The first of these, stereoselectivity, is of most relevance in the mono-addition of disubsituted alkynes and non-symmetrical allenes, which give products with either *E* or *Z* alkenes. The *anti*-attack of the nucleophile to the gold (Scheme 1.2) helps to define this *E*/*Z* selectivity in the product, but for 1,3-disubstituted allenes, as discussed later (Chapter 2), the face on which the nucleophile attacks (Figure 1.2, **1.20**) also defines the *E*/*Z* selectivity of the product. Chemoselectivity is also an issue as single or double addition is possible in both alkynes

and allenes. Finally, there is a question of regioselectivity, as either the Markovnikov or anti-Markovnikov products could be obtained. In terminal alkynes this equates to the nucleophile adding to either the substituted or non-substituted end of the alkyne whereas in allenes the nucleophile can add to either carbon a or b (Figure 1.2, **1.18**).

There is another kind of regioselectivity in allenes which is not found in alkynes. For the purposes of differentiating between the two kinds of regioselectivity, in this thesis the selectivity between carbon a and c will be referred to as positional selectivity (Figure 1.2, **1.19**). This positional selectivity occurs because the gold catalyst can activate either of the two adjacent carbon-carbon double bonds and so the nucleophile can attack either carbon a or c (Figure 1.2, **1.19**).[34] Another form of selectivity not found in alkynes, but that is present in enantioenriched 1,3-disubstituted allenes, is the selective attack at either the upper or lower face of the allene (Figure 1.2, **1.20**). In order for chirality transfer to take place, the nucleophile must preferentially attack either the upper or lower face of the allene.

1.3.3 Intermolecular hydrofunctionalisation of mono-substituted allenes

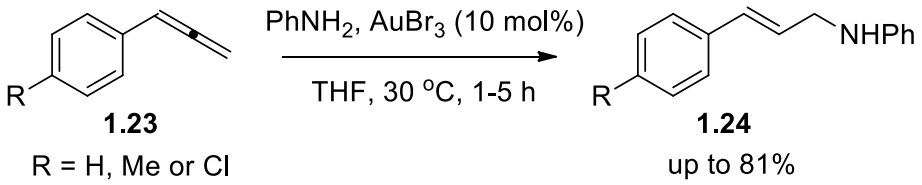
Despite the selectivity issues discussed above, there are still many examples of gold-catalysed hydrothiolations, hydroaminations, hydroalkoxylations and hydroarylations, which give only one product. The hydrothiolation example below (Scheme 1.8) shows a double addition at the central carbon of allene **1.21** under gold(III)-catalysed conditions to give product **1.22** in good yield.



Scheme 1.8: Gold(III)-catalysed hydrothiolation of allenes[35]

Interestingly, the regioselectivity (Figure 1.2, **1.18**) of this gold-catalysed hydrothiolation (Scheme 1.8) is unlike that reported for similar hydrofunctionalisation reactions. When amines, alcohols and aryls are used as nucleophiles, the reaction would be expected to occur at the outer carbons of the allene.

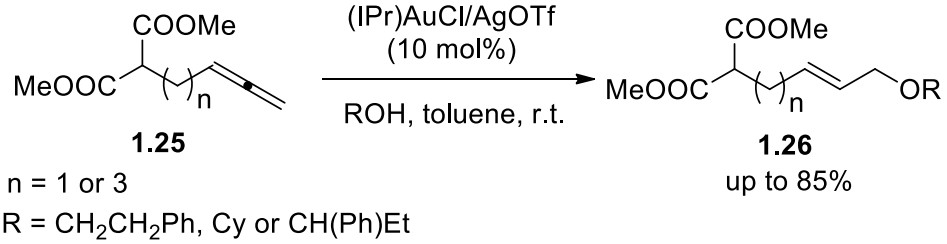
In the following hydroamination example (Scheme 1.9), a single nucleophile is added to the least substituted outer carbon of the allene **1.23**. The reaction proceeds under gold(III)-catalysed conditions to give product **1.24** in excellent yield.[36]



Scheme 1.9: Gold(III)-catalysed hydroamination of a mono-substituted allenes[36]

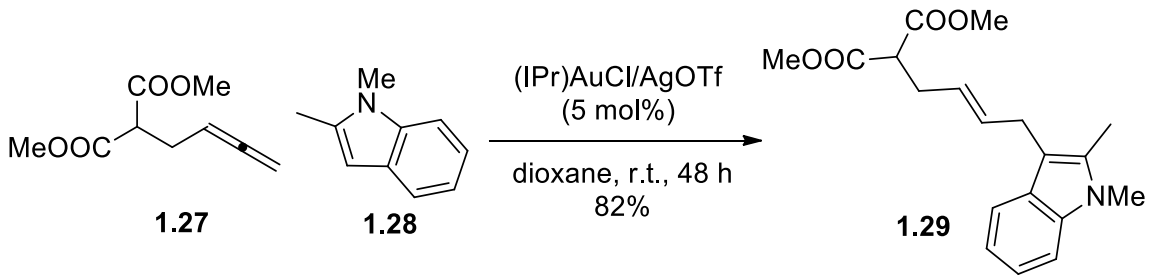
These gold-catalysed hydrothiolations and hydroaminations differ in both chemoselectivity and regioselectivity, with a double addition of the nucleophile at the central carbon in hydrothiolations (Scheme8) and a single addition to an outer carbon in hydroaminations (Scheme 1.9).

The selectivity reported in hydroamination (Scheme 1.9) is also reported for the hydroalkoxylation of allene **1.25**. The reaction is catalysed by a gold(I) species and gives the product **1.26** in good yield (Scheme 1.10).[37]



Scheme 1.10: Gold(I)-catalysed hydroalkoxylation of mono-substituted allenes[37]

Hydroarylation of similar mono-substituted allene **1.27** with indole **1.28** proceeds in excellent yield and again reacts at the terminal carbon of the allene (Scheme 1.11).[38] The latter was found to be the case for all other reported hydroarylations of mono-substituted allenes using arenes as the nucleophile.[39, 40]

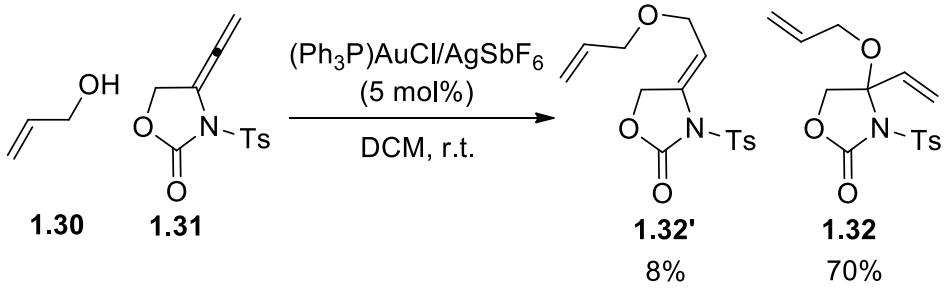


Scheme 1.11: Gold(I)-catalysed hydroarylation of a mono-substituted allene[38]

As well as the same chemoselectivity and regioselectivity in these hydroamination, hydroalkoxylation and hydroarylation reactions with mono-substitued allenes, the same positional selectivity is also observed. Interestingly, the examples of hydroamination (Scheme 1.9) and hydroalkoxylation reactions (Scheme 1.10) are taken from literature reports which show examples of hydrofunctionalisation reactions with 1,1-disubstituted and 1,1,3-trisubstituted allenes. They report that the positional selectivity for the least substituted carbon-carbon bond of the allene is the same for all these allene types. However, it was later shown that the positional selectivity can be switched in the hydroalkoxylation of 1,1-disubtituted allenes.

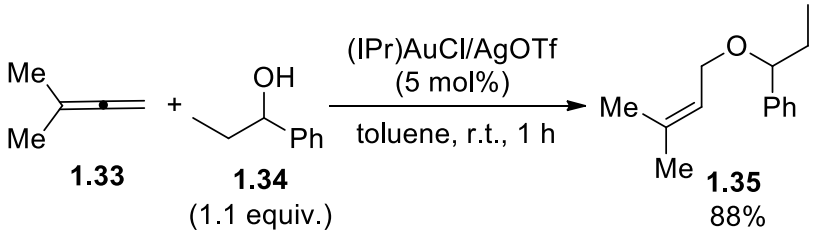
1.3.4 Positional selectivity in hydroalkoxylation of 1,1-disubstituted allenes

Unlike the hydroamination reaction, where positional selectivity for the least substituted end of the allene is found in all cases,[36, 41, 42] the related hydroalkoxylation of allenes is not as straightforward and required further investigation. Among the first reports of intermolecular hydroalkoxylation was the following example by Horino *et al.* (Scheme 1.12) where the allyl alcohol **1.30** was preferentially added to the more substituted end of allene **1.31**.[43]

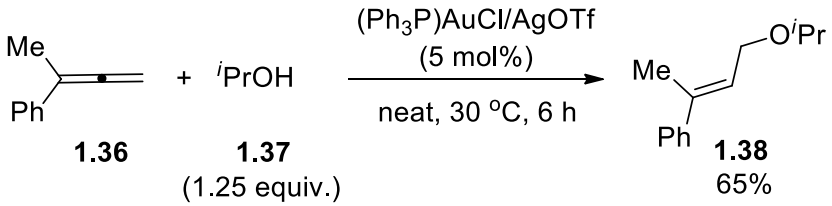


Scheme 1.12: Early example of hydroalkoxylation at most substituted end of allene[43]

However, other reports at the time, using more general substrates, showed selective attack at the least substituted end of the allene to give the primary allylic ether. For example, the following conditions reported by Widenhoefer and co-workers[37] (Scheme 1.13) and Yamamoto & co-workers[41, 44] (Scheme 1.14) produced good yields and high selectivity for a range of substrates.



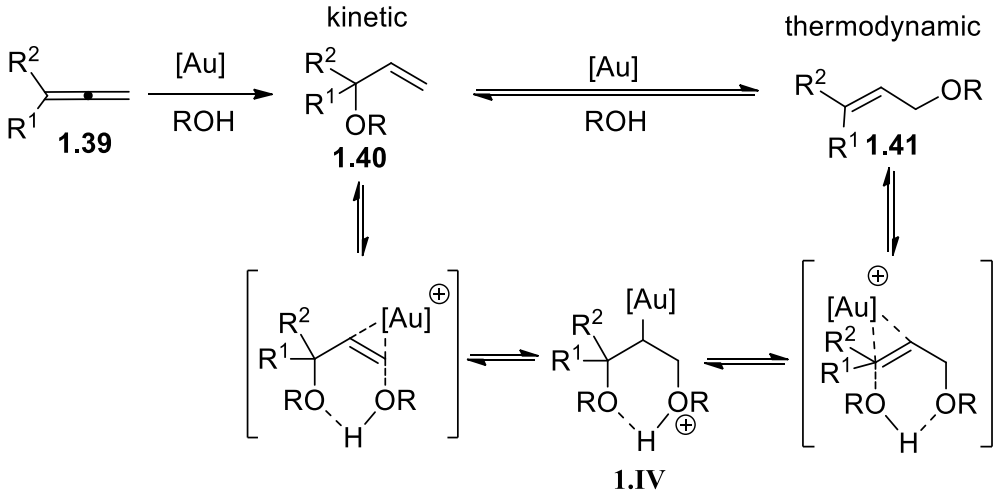
Scheme 1.13: Hydroalkoxylation of 1,1-disubstituted allene – Widenhoefer's conditions[37]



Scheme 1.14: Hydroalkoxylation of 1,1-disubstituted allene – Yamamoto's conditions[41, 44]

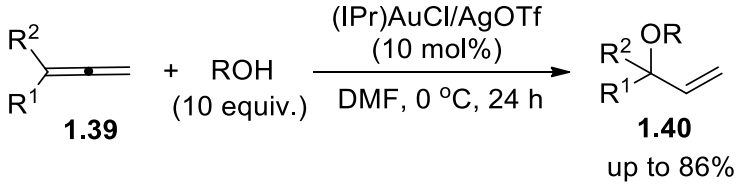
Shortly after these experimental observations (Scheme 1.13 and Scheme 1.14), Paton and Maseras reported their computational investigations on this system.[45] Initially, they found that their results were in agreement with what was found experimentally. Their computational results suggested that coordination of the gold catalyst to the less substituted end of the allene is energetically favoured, a result later confirmed by variable temperature NMR studies conducted by Widenhoefer.[46] However, as Paton and Maseras furthered their investigation, they found that nucleophilic attack at the more substituted end of the allene to give the tertiary allylic ether product **1.40** (Scheme 1.15) was in fact kinetically favoured. Experimentally, however, Widenhoefer[37] (Scheme 1.13) and Yamamoto[41, 44] (Scheme 1.14) isolated the primary

allylic ether **1.41** as the sole product. Paton and Maseras therefore suggested that the primary allylic ether **1.41** (Scheme 1.15), which was found to be the thermodynamic product in their studies, was isolated experimentally due to subsequent isomerisation of the kinetic product **1.40**. Their computational studies suggest that the kinetic product **1.40** is formed, and then gold-catalysed attack of a second alcohol molecule gives the intermediate **1.IV**. This intermediate then loses an alcohol molecule to yield the thermodynamic primary allylic ether product **1.41** observed experimentally.



Scheme 1.15: Isomerisation proposed by DFT calculations[45]

In 2010, the Lee group provided experimental evidence to support this theory by successfully developing conditions that suppressed the isomerisation of **1.40** to **1.41** (Scheme 1.16).[47] As a result, the selectivity was successfully switched for the first time from the primary (**1.41**, Scheme 1.15) to the tertiary allylic ether product **1.40** (Scheme 1.16).



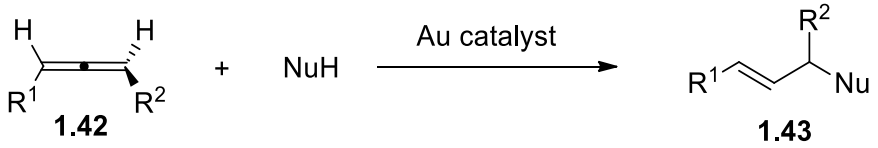
Scheme 1.16: Conditions used by the Lee group to give the kinetic product[47]

The development of these conditions and their use as a means to prevent a secondary, undesired gold-catalysed reaction is of great importance to the projects discussed in

Chapters 2 and 3. More detail as to development and application of these conditions will be given in Chapters 2 and 3.

1.3.5 Chirality transfer in hydrofunctionalisation of allenes

As well as the other forms of selectivity previously mentioned, there is also the possibility for chirality transfer in the hydrofunctionalisation of allenes. Since 1,3-disubstituted allenes possess axial chirality,[48] if the face on which the nucleophile is added is controlled, then chirality from enantioenriched allenes can be transferred to the product. Since the product has point chirality, this is defined as axial-to-point chirality transfer.[48] The possibility of chirality transfer makes 1,3-disubstituted allenes very interesting substrates for hydrofunctionalisation reactions. However, when compared to mono-substituted and 1,1-disubstituted allenes, 1,3-disubstituted allenes have been far less studied. This may be due to positional selectivity issues (Figure 1.2), as unlike the mono-substituted and 1,1-disubstituted allenes, 1,3-disubstituted allenes do not have a more substituted end. Instead, positional selectivity is dependent on R^1 and R^2 being sufficiently different to give selective addition at one end of the allene. Therefore, to obtain one positional isomer *and* achieve chirality transfer, the nucleophile must selectively attack one of the carbon-carbon bonds of the allene and must do so with facial selectivity. Despite these challenges, hydroamination of 1,3-disubstituted allenes has been achieved for nitrogen containing nucleophiles with excellent chirality transfer (Table 1.1).

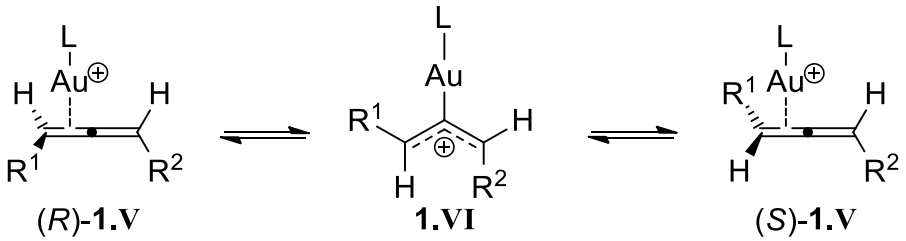


Entry	R^1	R^2	NuH	e.e. (%) **1.42**	Conditions (mol%)	yield (%)	e.e. (%) **1.43**
1[36]	Ph	Me	$PhNH_2$ (2 eq.)	94	$AuBr_3$ (10) THF, 30 °C	68	88
2[36]	$(CH_2)_4CH_3$	$(CH_2)_4CH_3$	$PhNH_2$ (2 eq.)	99	$AuBr_3$ (10) THF, 30 °C	80	99
3[41]	$(CH_2)_4CH_3$	$(CH_2)_4CH_3$	Morpholine (1.2 eq.)	96	(**L1**)AuCl/AgOTf (10) toluene, 80 °C	74	55
4[49]	$(CH_2)_2Ph$	$(CH_2)_2Ph$	NH_2NHCO_2Me (4 eq.)	87	$(Ph_3P)AuNTf_2$ (6) $MeNO_2$, 45 °C	81	56

L1 = (Ph_2(*o*-tolyl)P)

Table 1.1: Chirality transfer in the hydroamination of 1,3-disubstituted allenes

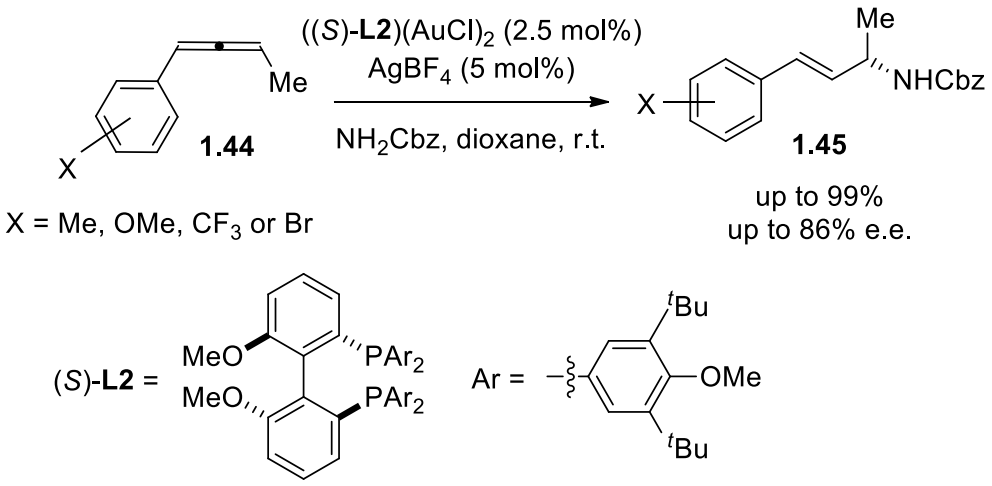
Yamamoto and co-workers first reported two examples of excellent chirality transfer in the hydroamination of allenes with aniline (Entries 1-2, Table 1.1)[36]. The same group later reported a similar reaction but this time using morpholine as the nucleophile and employing more forcing conditions (Entry 3, Table 1.1).[41] Unfortunately, perhaps due to the more forcing conditions required, the hydroamination of allenes with morpholine gave much poorer chirality transfer. Finally, Toste and co-workers reported the use of a hydrazide as a nucleophile, however, the chirality transfer achieved is more modest under their conditions (Entry 4, Table 1.1).[49] These reports demonstrate that chirality transfer in the hydroamination of allenes is indeed possible but also shows that there is often substantial erosion of e.e. All of the reports described in Table 1.1 suggest that racemisation of the starting material allene is the cause for the erosion of e.e. and indeed it has been shown that the allenes are quickly racemised under gold-catalysed conditions.[41, 44]



Scheme 1.17: Gold-catalysed 1,3-disubstituted allene racemisaton

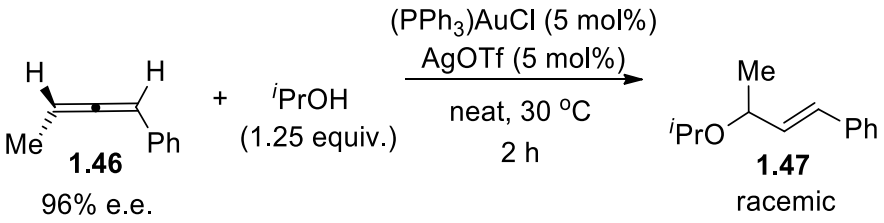
The mechanism by which enantioenriched allenes are thought to be racemised under gold-catalysed conditions begins with the coordination gold catalyst to the allene (**1.V**, Scheme 1.17). The gold catalyst is then thought to slip to the central carbon of the allene bringing the two R-groups into the same plane (**1.VI**, Scheme 1.17) and so allowing for racemisation.

Allene racemisation through this mechanism (Scheme 1.17) presents a major challenge to achieving chirality transfer in the hydrofunctionalisation of enantioenriched 1,3-disubstituted allenes.[50] Ingeniously however, Widenhoefer and co-workers took advantage of the gold-catalysed racemisation of allenes in their report (Scheme 1.18).[51] Using racemic aryl allenes rather than enantioenriched substrates and a di-gold chiral catalyst, they report the enantioselective hydroamination of allenes to give products with high e.e. Reactions of this type, where the catalyst selectively reacts with one enantiomer, would usually have a maximum possible yield of 50%. However, since the catalyst also racemises the allene starting material, high yields are obtained in this reaction (Scheme 1.18).



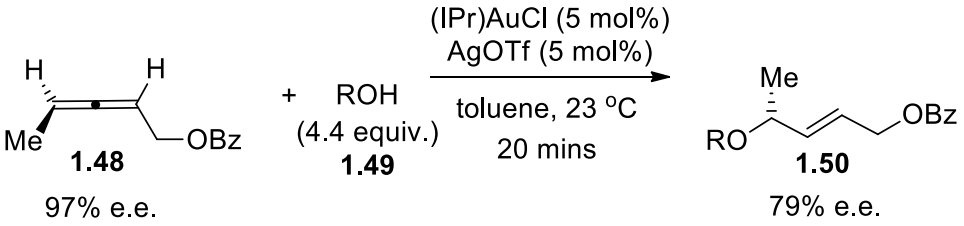
Scheme 1.18: Enantioselective hydroamination of racemic 1,3-disubstituted allenes[51]

Although allene racemisation has posed a challenge, chirality transfer in the hydroamination of 1,3-disubstituted allenes has been achieved for some selected substrates (Entry 2, Table 1.1). In contrast, allene racemisation is a much bigger problem in gold-catalysed hydroalkoxylation of allenes and has prevented progress in this field. For example, Yamamoto and co-workers found that even in systems where chirality transfer in hydroamination worked well (Entry 1, Table 1.1), hydroalkoxylation of the same allene (**1.46**) yielded only racemic product (Scheme 1.19).[41, 44]



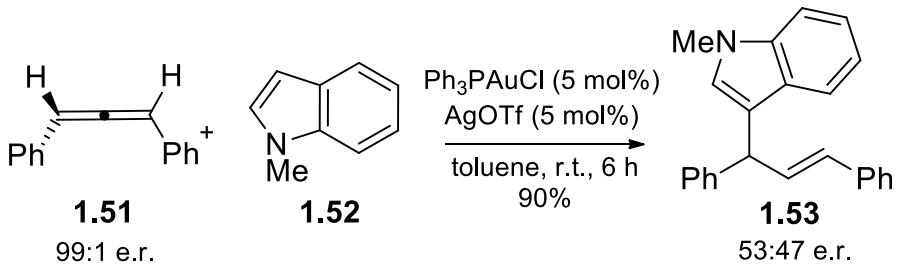
Scheme 1.19: Unsuccessful attempt at chirality transfer in hydroalkoxylation[41, 44]

Yamamoto and co-workers suggest that allene racemisation is more of an issue in hydroalkoxylation reactions than hydroamination reactions because alcohols are less nucleophilic than *N*-nucleophiles. This difference in nucleophilicity makes the hydrofunctionalisation slower in hydroalkoxylation reactions, thereby exacerbating the problem of competitive gold-catalysed allene racemisation.[41]



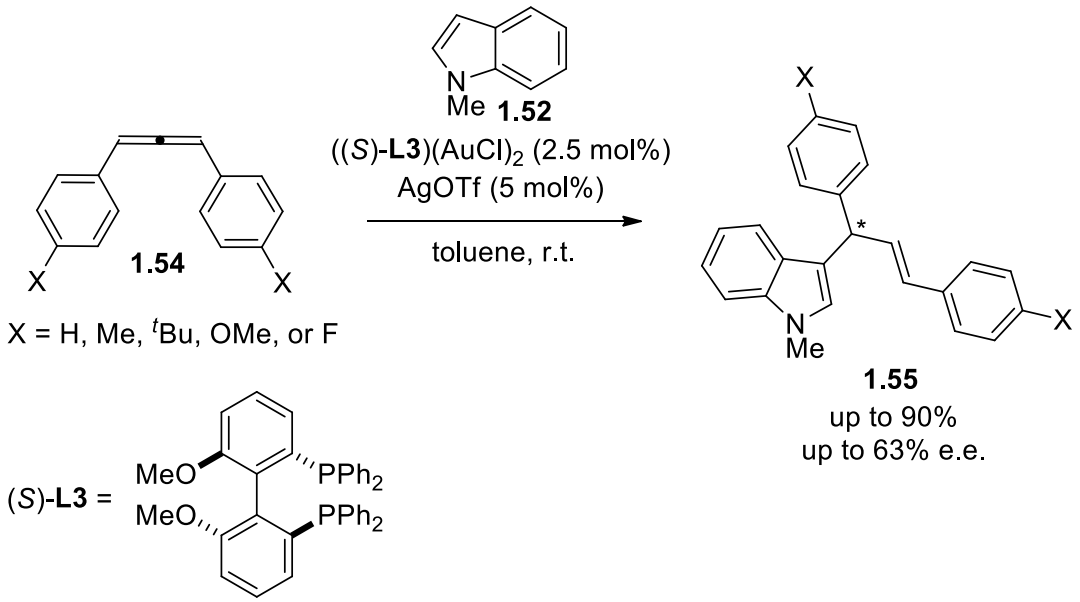
Scheme 1.20: Widenhoefer's chirality transfer in hydroalkoxylation[37]

Encouragingly, Widenhoefer and co-workers had more success with achieving chirality transfer in the hydroalkoxylation of allenes, but published only one example, using allene **1.48** (Scheme 1.20). Although chirality transfer does occur, the reaction proceeded with substantial erosion of enantiomeric excess (97% e.e. to 79% e.e., Scheme 1.20) showing that allene racemisation is a much greater challenge in the hydroalkoxylation of allenes than it was found to be in the hydroamination of allenes. Similarly, chirality transfer in the hydroarylation of allenes is not nearly as well documented, with the only attempt being reported by Che and coworkers and their conditions providing almost totally racemic product (Scheme 1.21).[52]



Scheme 1.21: Hydroarylation of enantioenriched allene – Che's initial conditions[52]

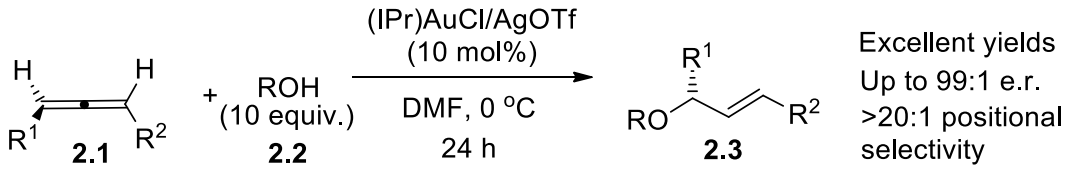
Che and co-workers were able to overcome the challenge of starting material racemisation by instead developing the first chiral digold-catalysed enantioselective hydroarylation reaction. Under Che's conditions, racemic symmetrical diaryl allene starting materials were reacted with indoles in up to 90% yield. However, the best enantioselectivity accomplished was only 63% e.e.[52] (Scheme 1.22) and importantly this was achieved using a chiral catalyst rather than chirality transfer from the allene.



Scheme 1.22: Enantioselective hydroamination of racemic 1,3-disubstituted allenes[52]

Prior to the projects detailed in Chapters 2 and 3, the reports discussed in this section were the only attempts at chirality transfer in intermolecular gold-catalysed hydroalkoxylation and hydroarylation of allenes. Therefore there is clear scope for improvement in this area, with the main challenge being the competing racemisation of the allene substrate.

Chapter 2: Chirality transfer in the gold-catalysed hydroalkoxylation of allenes



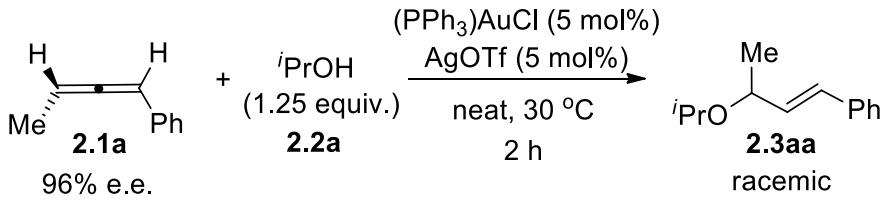
Acknowledgments

The author would like to thank Stacey Webster for her collaboration on this project. All work completed by Stacey is clearly marked with ϖ. Substrates which were made by Stacey for this project and later synthesised by the author are marked with (ϖ). In these cases, the yields and experimental detail reported are from experiments completed by the author.

2.1 Introduction

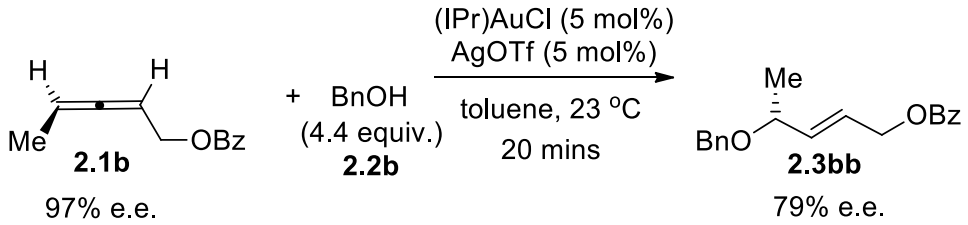
2.1.1 Previous work in the hydroalkoxylation of allenes

As discussed in Chapter 1, the gold-catalysed hydroalkoxylation of allenes, and hydrofunctionalisation of allenes generally, has been extensively investigated. However, in hydroalkoxylation reactions, much of the attention has been focused on intramolecular reactions to form heterocyclic products.[1] Any investigation which has been done on intermolecular reactions has focused mainly on 1-substituted and 1,1-disubstituted allenes.[37, 41, 44, 47] However, 1,3-disubstituted allenes (**2.1**) are of particular interest due to the possibility of axial-to-point chirality transfer. This has been investigated with some success for hydroamination.[36, 41, 42, 44, 49, 51] However, chirality transfer in hydroalkoxylation of 1,3-disubstituted allenes has been far less successfully investigated, with only two attempts being published. The first attempt was by Yamamoto and co-workers who reported totally racemic product (Scheme 2.1).[41, 44]



Scheme 2.1: Unsuccessful attempt at chirality transfer in hydroalkoxylation[41, 44]

Another, more promising result, was reported by Widenhoefer and co-workers who showed some chirality transfer but with substantial erosion of e.e. (Scheme 2.2).[37]



Scheme 2.2: A more successful attempt at chirality transfer in hydroalkoxylation[37]

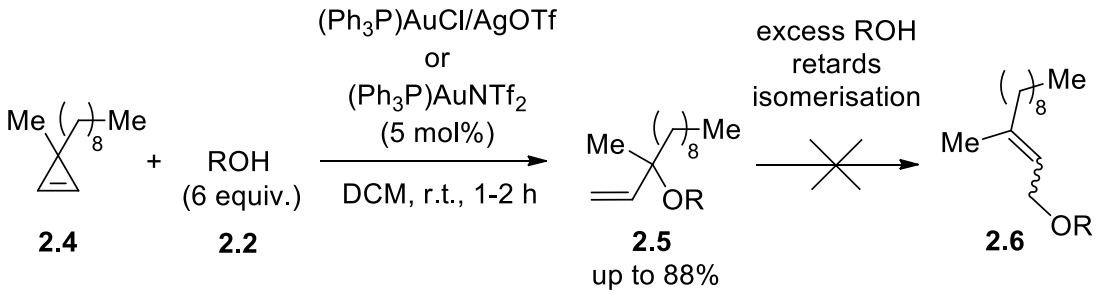
In both cases, racemisation of the starting material allene was cited as the reason for the lack of, or poor, chirality transfer. This remains an unsolved problem and a clear

limitation in this field. One possible solution to this challenge would be to develop conditions in which the gold catalyst is reactive enough to catalyse the hydroalkoxylation reaction but not the unwanted allene racemisation. The Lee group have experience in the field of selective gold catalysis and have shown many examples of how conditions can be adapted to drive one gold-catalysed reaction over another.

2.1.2 The Lee group's work in selective gold catalysis

Previous work in the Lee group has demonstrated that several experimental conditions can be altered to give excellent selectivity in gold-catalysed reactions. Discussed below are some examples where the product obtained was controlled by adapted conditions to retard a secondary, unwanted and often gold-catalysed reaction.

In the following example, the Lee group successfully prevented the gold-catalysed isomerisation of the desired tertiary alkylic ether product (**2.5**) in their investigations on gold-catalysed reactions with cyclopropenes (Scheme 2.3).[53]

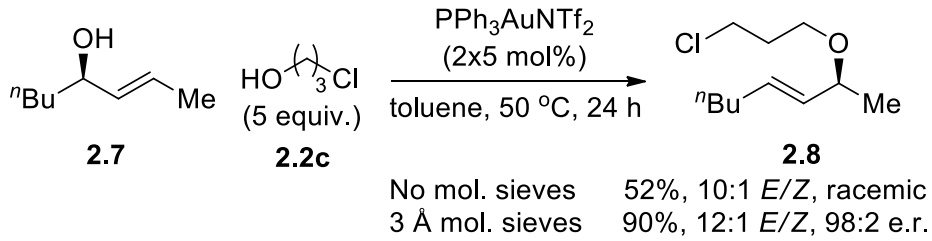


Scheme 2.3: Selective gold(I)-catalysed alcohol additions to cyclopropenes giving *tert*-allylic ether[53]

It was found that the kinetic product of the gold-catalysed addition of alcohols to cyclopropenes (**2.4**) is readily isomerised to the primary allylic ether **2.6** under gold-catalysed conditions. However, this isomerisation can be prevented by increasing the equivalents of alcohol in the reaction. In order to investigate this further, the Lee group resubjected the tertiary allylic ether product **2.5** to the reaction conditions with no alcohol present. It was found that the tertiary allylic ether product **2.5** is quickly isomerised to the primary allylic ether **2.6**. However, if the tertiary allylic ether **2.5** is resubjected to the reaction conditions with 5 equivalents of alcohol present, no

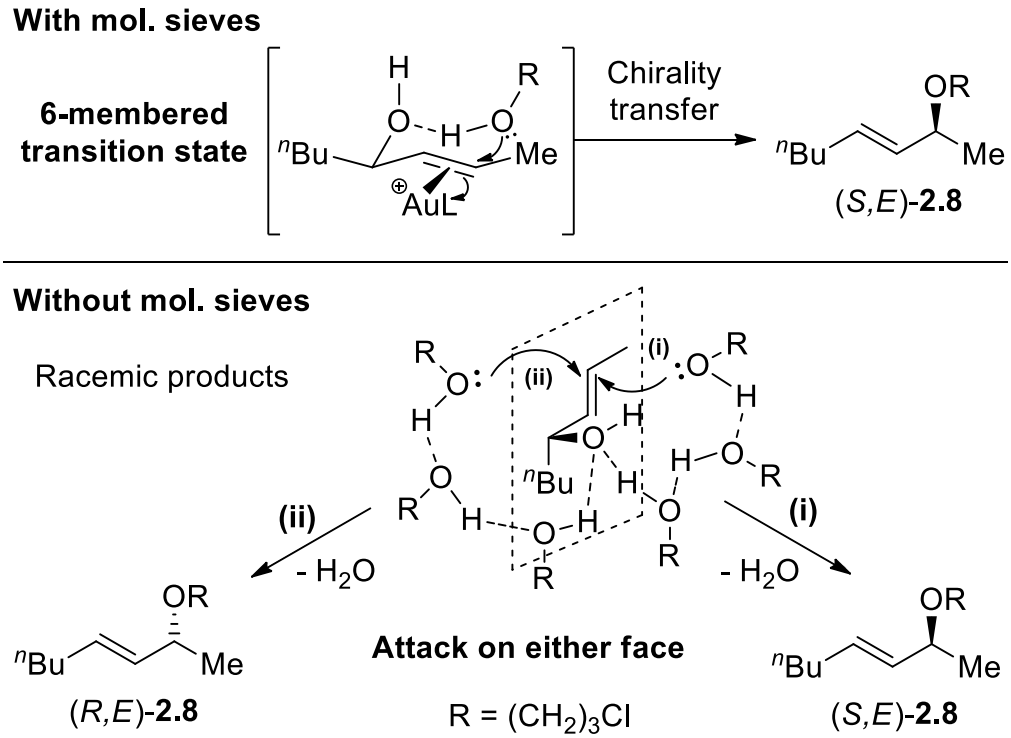
isomerisation to **2.6** takes place. This result confirms that the excess alcohol is preventing isomerisation, likely by coordinating to the gold catalyst and dampening its reactivity.[53]

Later work showed the use of molecular sieves to achieve chirality transfer in gold(I)-catalysed direct allylic etherifications of unactivated alcohols (Scheme 2.4).[54]



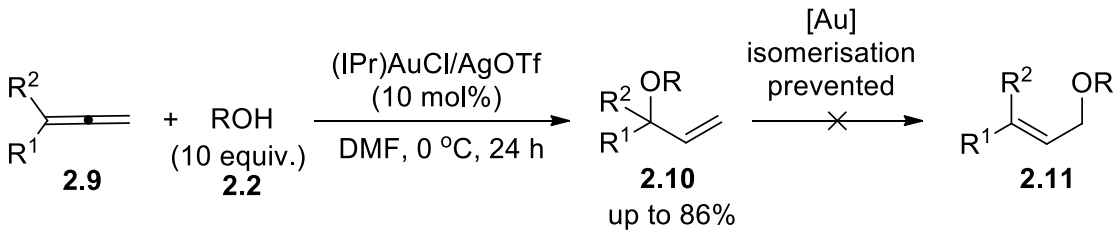
Scheme 2.4: Chirality transfer in direct allylic etherification using mol. sieves[54]

With the assistance of computational experiments, the Lee and Macgregor groups were able to suggest that the molecular sieves likely facilitate chirality transfer by disrupting the aggregation of alcohol molecules. The involvement of only one alcohol molecule allows efficient delivery of the alcohol nucleophile to one face of the alkene through a chair-like 6-membered transition state (Scheme 2.5). In contrast, when no molecular sieves are used, aggregation of alcohol molecules allows for attack at either face of the alkene (Scheme 2.5). Since attack of the nucleophile can occur on either face of the alkene, when aggregation of alcohol molecules is allowed, racemic product is obtained.



Scheme 2.5: Proposed mechanism for loss of chirality transfer without mol. sieves[54]

Most closely related to this project, and previously discussed in Chapter 1, is the allene hydroalkoxylation work reported in 2010 by the Lee group.[47] In this report, the Lee group successfully developed conditions which allowed for selective formation of the kinetic product from the hydroalkoxylation of 1,1-disubstituted allenes (**2.10**, Scheme 2.6). Computational studies[45] had suggested that the tertiary allylic ether product **2.10** was indeed the kinetic product of the reaction. However, in previous experimental reports, only the primary allylic ether **2.11** was ever isolated.[37, 41, 44] This was thought to be due to the subsequent gold-catalysed isomerisation of **2.10** to the thermodynamic product **2.11**. Nevertheless, the Lee group successfully developed conditions that suppressed this isomerisation, allowing isolation of the tertiary allylic ether **2.10** in up to 86% yield for a range of substrates (Scheme 2.6).



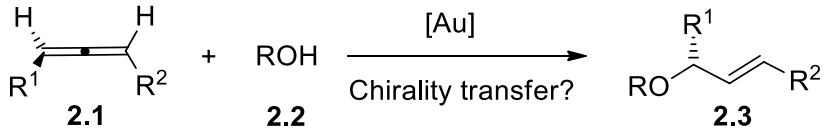
Scheme 2.6: Conditions used by the Lee group to give the kinetic product[47]

The conditions used in Scheme 2.6 were designed specifically to slow down the reactivity of the gold catalyst, thereby preventing the secondary isomerisation. Upon comparison with previously reported conditions[37, 41, 44] in which the isomerisation to the thermodynamic product **2.11** occurs, there appears to be three main differences. These differences are the higher number of equivalences of alcohol, lower temperature and the use of the coordinating solvent DMF. DMF and excess of alcohol are thought to reduce the activity of the active cationic gold catalyst (IPr)Au^+ through reversible coordination.[55] At the lower temperature of 0 °C, the resulting less active catalytic conditions are enough to catalyse the hydroalkoxylation of the allene **2.9** giving product **2.10**, but not active enough to catalyse the unwanted isomerisation to the thermodynamic product **2.11**.

The development of these different conditions to prevent a secondary gold-catalysed reaction is of great importance to the aim of this project. With the knowledge gained during the projects discussed in this section, we hoped to develop conditions to selectively allow for chirality transfer in hydroalkoxylation of 1,3-disubstituted allenes by supressing the racemisation of the allenes.

2.2 Project aims

The aim of this project is to develop the first hydroalkoxylation of 1,3-disubstituted allenes with efficient chirality transfer (Scheme 2.7).



Scheme 2.7: Is efficient chirality transfer in the hydoalkoxylation of 1,3-disustituted allenes possible?

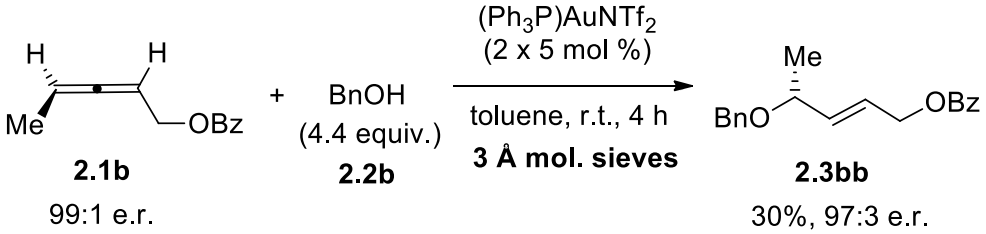
The main challenge is the competing gold-catalysed racemisation of the allene starting material **2.1**. Drawing upon the Lee group's experience in selective gold catalysis, we hope to achieve this by adapting the conditions described in Section 2.1.2 to allow the gold-catalysed hydroalkoxylation reaction to occur without the unwanted gold-catalysed allene racemisation.

Upon developing conditions for good chirality transfer, we aim to investigate the substrate and nucleophile scope of the reaction. By investigating the substrate scope we hope to better understand the prerequisites for achieving good chirality transfer as well as positional selectivity, and to better understand the mechanism of the reaction.

2.3 Results and Discussion

2.3.1 Optimisation of the hydroalkoxylation reaction

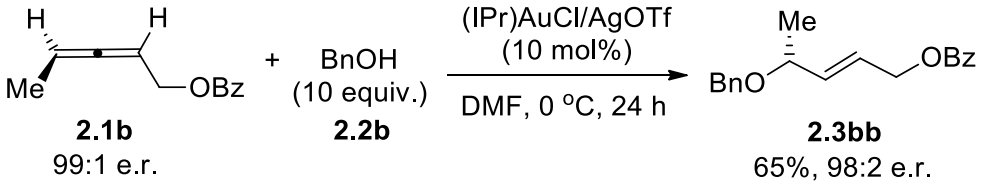
The initial approach used by the Lee group to supress allene racemisation and therefore facilitate chirality transfer was to add molecular sieves to the reaction (Scheme 2.8). This approach was inspired by previous work on gold-catalysed allylic etherification, where molecular sieves were crucial for efficient chirality transfer.[54] Allene **2.1b** and alcohol **2.2b** were adopted for these trial reactions to allow a direct comparison with previously published results by Widenhoefer.[37]



Scheme 2.8: Trial conditions with molecular sieves[ϖ]

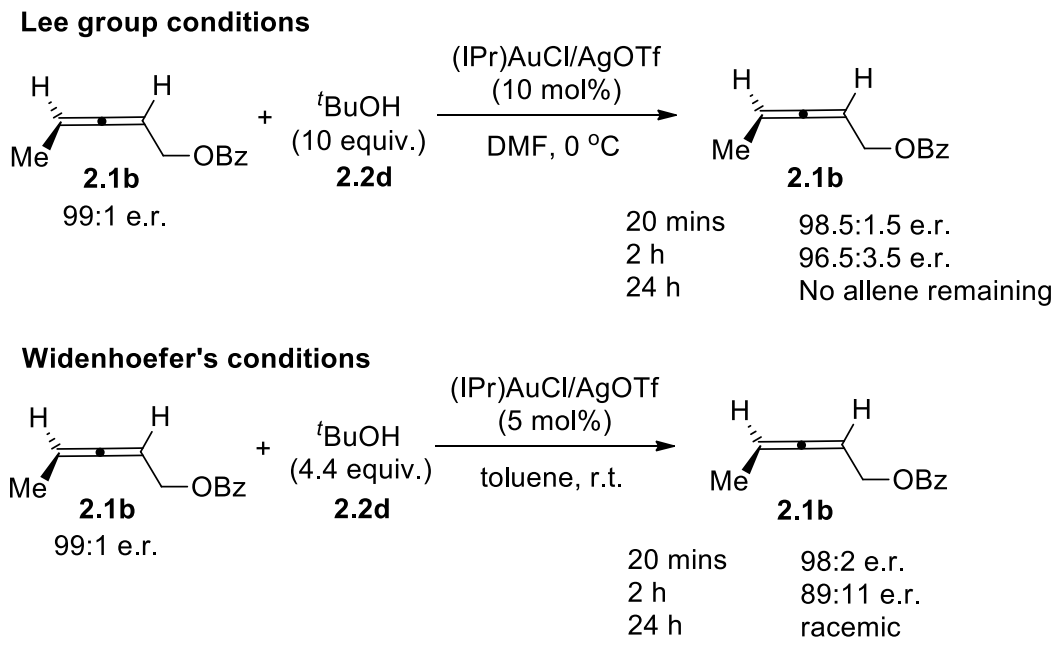
The results obtained under these conditions were promising, providing a higher degree of chirality transfer to the product (**2.3bb**, 97:3 e.r.) than that reported by Widenhoefer (**2.3bb**, 90:10 e.r., Scheme 2.2).[37] However, the yield was only 30% and attempts at optimisation by increasing the time, temperature and catalyst loading did not significantly improve the yield without a decrease in chirality transfer.

The second approach investigated made use of conditions previously reported in the Lee group (Scheme 2.6).[47] Since these conditions successfully catalysed the hydroalkoxylation of 1,1-disubstituted allenes while supressing unwanted isomerisation of the product, it was hypothesised that the conditions may also allow for the hydroalkoxylation of 1,3-disubstituted allenes while supressing racemisation of the starting material.



Scheme 2.9: Trial with previously reported conditions[ϖ]

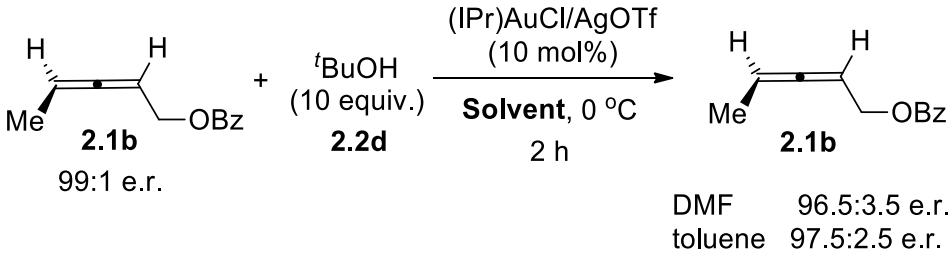
Pleasingly, excellent chirality transfer and a much more respectable yield of 65% were observed using these conditions (Scheme 2.9). To investigate whether these conditions were indeed giving better chirality transfer by preventing the racemisation of the allene substrate, control reactions were carried out. These control reactions compared the new conditions (Scheme 2.9) with those reported by Widenhoefer[37] (Scheme 2.2). First, the product **2.3bb** was resubjected to the reaction conditions and it was found that under both conditions the product **2.3bb** showed no or very little erosion of e.r., suggesting that this is not the major cause of e.r. erosion in the gold-catalysed hydroalkoxylation reaction. Control reactions with the allene **2.1b** were also carried out, which showed that the allene **2.1b** completely racemised under both conditions. However, these initial control reactions were done with no alcohol present, which does not accurately reflect the reaction conditions in which excess alcohol is always present. The control reactions were therefore repeated in the presence of ^{t}BuOH (**2.2c**) to give a more accurate representation of the reaction conditions (Scheme 2.10). Since ^{t}BuOH (**2.2c**) is sterically hindered, it reacts very slowly with allene **2.1b**, allowing the racemisation to monitored.



Scheme 2.10: Racemisation of allene control reactions[ϖ]

The control reactions clearly show that the allene **2.1b** racemises faster under Widenhoefer's conditions and that allene racemisation is indeed the reason for the erosion of e.r. in the product.

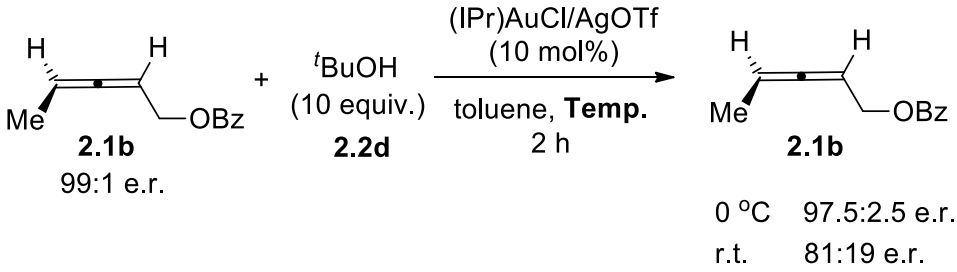
Next, investigations were carried out to determine whether the solvent, temperature, equivalents of alcohol or a combination of these factors was causing the difference in the rate of allene racemisation. First, in order to investigate the effect of solvent, allene **2.1b** was subjected to the reaction conditions in the presence of ^{t}BuOH and with toluene as the solvent rather than DMF (Scheme 2.11).



Scheme 2.11: Investigation into the effect of solvent on allene racemisation[ϖ]

After two hours, the resulting enantiomeric ratios were within error of each other, suggesting that the solvent is not the most crucial change. The temperature was then

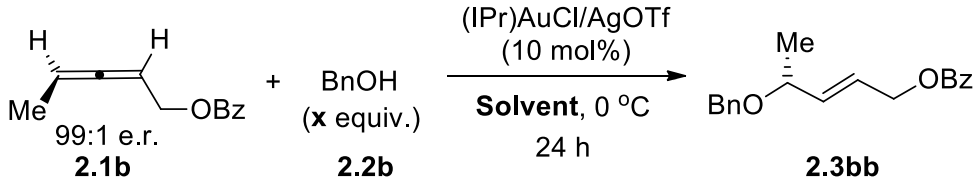
investigated by carrying out the same control reaction at room temperature rather than 0 °C (Scheme 2.12).



Scheme 2.12: Investigation into the effect of temperature on allene racemisation[ϖ]

This control reaction showed that increasing the temperature to room temperature from 0 °C caused a substantial drop in e.r. after two hours (0 °C, 97.5:2.5 e.r. *vs.* r.t., 81:19 e.r., Scheme 2.12).

With these two results in mind, the gold-catalysed hydroalkoxylation reaction with allene **2.1b** was carried out with toluene as solvent and at 0 °C (Entry 2, Table 2.1). It was found that when compared to the original conditions (Entry 1, Table 2.1) the change in solvent had a very small effect on the e.r. of the product and increased the yield. Next, the effect of alcohol concentration was investigated (Entries 3-5, Table 2.1). Decreasing the equivalents of alcohol to 4 equiv. had no effect on the e.r. of product **2.3bb** but any further drop in equivalents of alcohol gave a decrease in chirality transfer (Entries 4-5, Table 2.1).

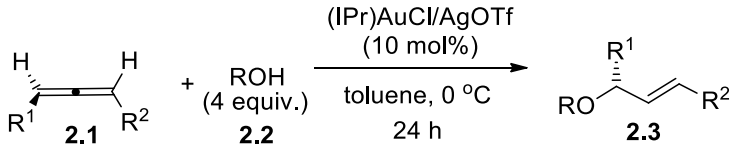


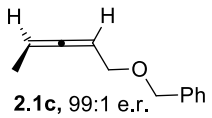
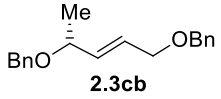
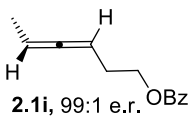
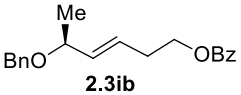
Entry	Solvent	BnOH equiv.	e.r.[a]	Yield (%)
1	DMF	10	98:2	65
2	Toluene	10	97:3	81
3	Toluene	4	97:3	85
4	Toluene	2	96:4	78
5	Toluene	1.1	93:7	74

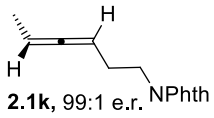
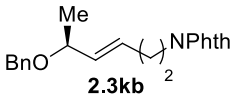
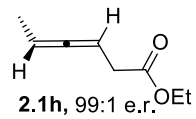
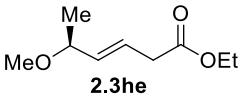
[a] Determined by CSP-HPLC.

Table 2.1: Effect of solvent and alcohol equiv. on the hydroalkoxylation of **2.1b**[ϖ]

The new conditions optimised for allene **2.1b** (Entry 3, Table 2.1), which gave excellent chirality transfer and yield with lower alcohol concentration, were then ready to be used as optimised conditions for the substrate scope. However, it was soon discovered that these conditions (Entry 3, Table 2.1) were very substrate specific, only giving good e.r. for product **2.3bb**. The original conditions (Entry 1, Table 2.1) consistently gave better chirality transfer or yield in all other allenes subjected to these conditions (Table 2.2 *vs.* Table 2.3) and were therefore more general.

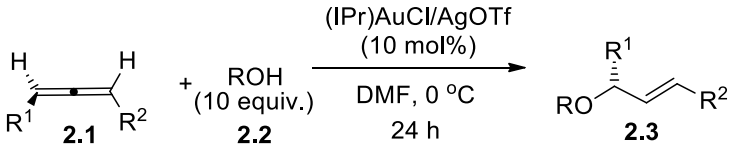


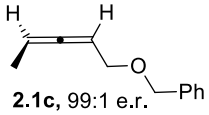
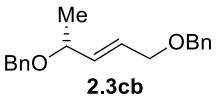
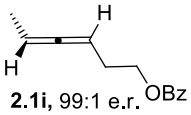
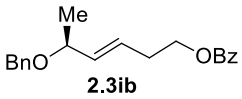
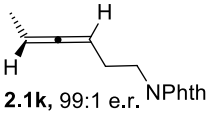
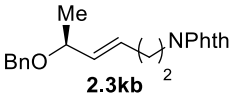
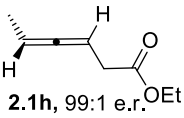
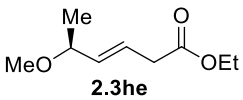
Entry	Allene	Alcohol	Product	Yield[a]	e.r.[b]
1[ϖ][c]	 **2.1c**, 99:1 e.r.	BnOH **2.2b**	 **2.3cb**	61%	87:13
2	 **2.1i**, 99:1 e.r.	BnOH **2.2b**	 **2.3ib**	70%	78:22

3	 **2.1k**, 99:1 e.r.	BnOH **2.2b**	 **2.3kb**	79%[d] 7:1 pos.	78:22
4	 **2.1h**, 99:1 e.r.	MeOH **2.2e**	 **2.3he**	63%	97:3

[a] Isolated yields, >20:1 E:Z and positional selectivity by ^{1}H NMR unless otherwise stated**. 2.2e** was used when the product using **2.2b** was not separable by CSP-HPLC, CSP-GC or chiral shift reagents. [b] Determined by CSP-HPLC [c] 2 equiv. alcohol [d] Combined yield.

Table 2.2: Substrates trialled with conditions optimised for **2.1b** in toluene



Entry	Allene	Alcohol	Product	Yield[a]	e.r.[b]
1[ϖ]	 **2.1c**, 99:1 e.r.	BnOH **2.2b**	 **2.3cb**	45%	95:5
2	 **2.1i**, 99:1 e.r.	BnOH **2.2b**	 **2.3ib**	79%	90:10
3	 **2.1k**, 99:1 e.r.	BnOH **2.2b**	 **2.3kb**	94%[c] 9:1 pos.	81:19
4	 **2.1h**, 99:1 e.r.	MeOH **2.2e**	 **2.3he**	92%	97:3

[a] Isolated yields, >20:1 E:Z and positional selectivity by ^{1}H NMR unless otherwise stated**. 2.2e** was used when the product using **2.2b** was not separable by CSP-HPLC, CSP-GC or chiral shift reagents. [b] Determined by CSP-HPLC [c] Combined yield.

Table 2.3: Substrates under original conditions (DMF) for comparison with Table 2.2

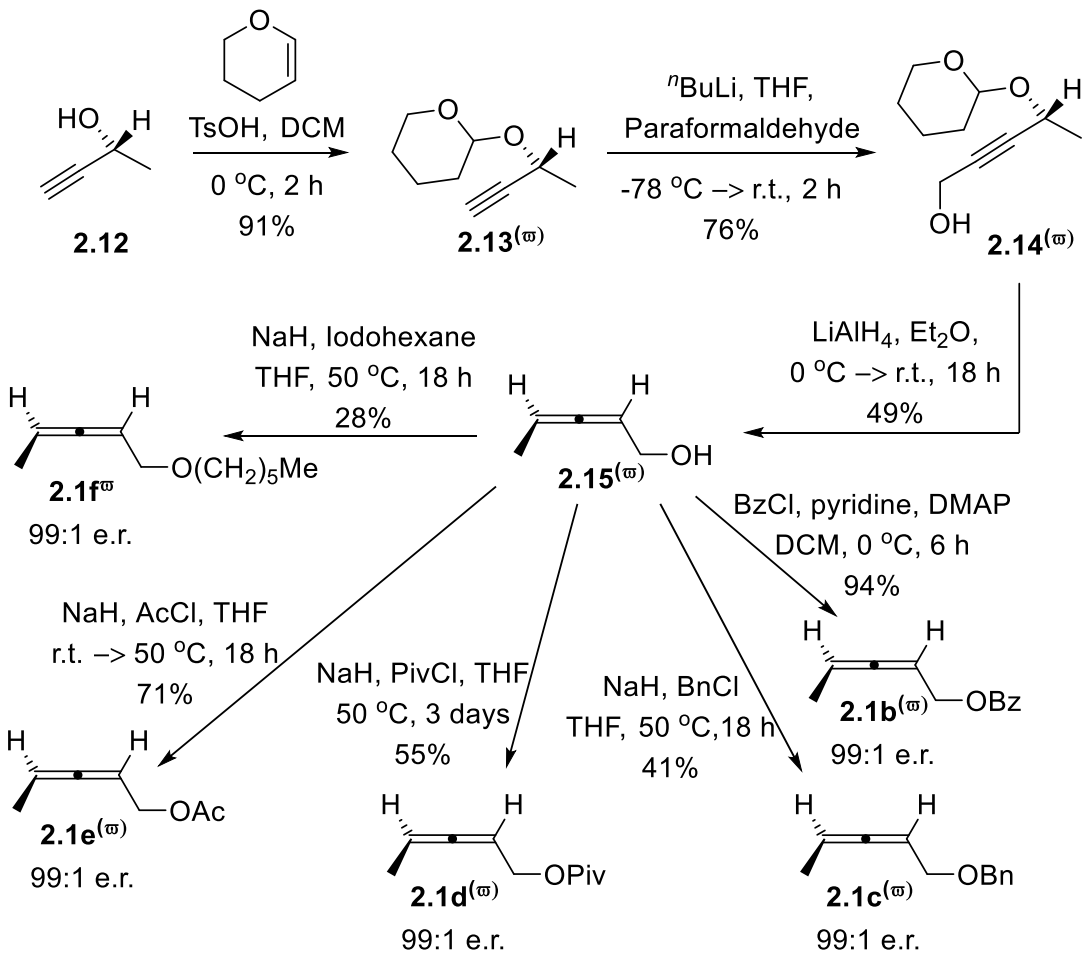
It was therefore concluded that these original conditions (Table 2.3) should be taken forward as optimised conditions for the full substrate scope. However, before

discussing the allene scope, a brief summary of how the enantioenriched allene substrates studied in this project were prepared has been included.

2.3.2 Substrate synthesis

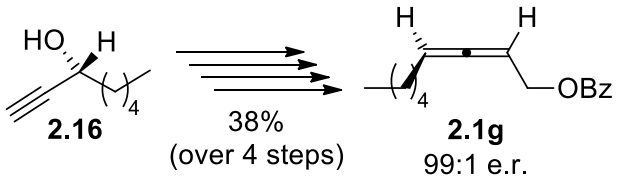
Perhaps the most commonly used synthetic route for the preparation of enantioenriched allenes starts with a commercially available enantioenriched propargylic alcohol. This starting point was used extensively during this project to give a range of allenes through the methods discussed below. However, the synthesis of enantioenriched 1,3-disubstituted allenes has been heavily investigated and a range of enantioenriched allenes can be made via a variety of strategies.[56] Racemic versions of each of the substrates were also made in order to determine the e.r. of the allene and products of the hydroalkoxylation. Unless otherwise stated this was achieved under the same conditions by starting with racemic starting material.

The majority of the allene substrates used in this project were made from (*R*)-1-butyn-3-ol **2.12** and the allenes which were first used as substrates were all made by conversion of (*R*)-1-butyn-3-ol to allenol **2.15** and subsequent protection giving substrates **2.1b** – **2.1f** (Scheme 2.13).[37]



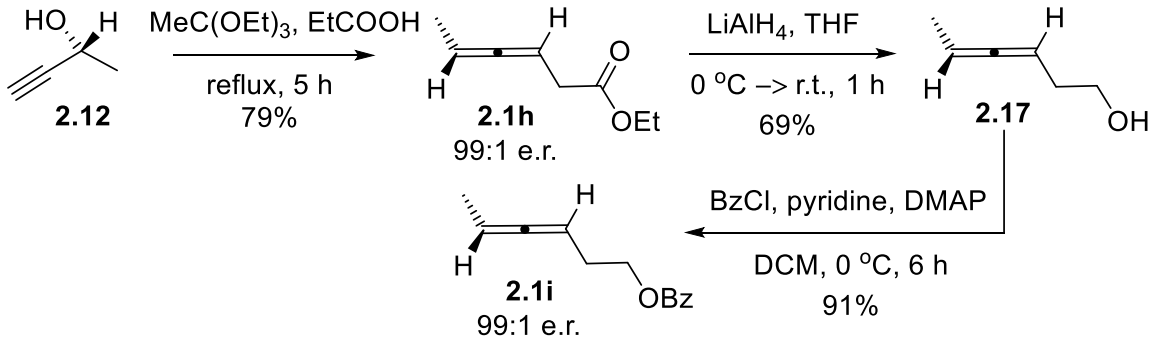
Scheme 2.13: Synthesis of protected allenol substrates **2.1b-2.1f**

Starting from (*R*)-1-octyn-3-ol **2.16** rather than (*R*)-1-butyn-3-ol **2.12** provided allene **2.1g** in good yield (Scheme 2.14) using the same conditions shown above (Scheme 2.13).



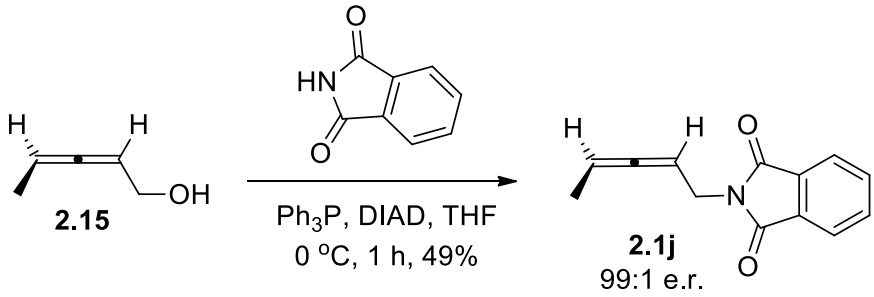
Scheme 2.14: Synthesis of substrate **2.1gϖ**

In order to test the effect of moving the functionality one CH_2 farther from the allene, substrate **2.1i** was prepared by conversion of (*R*)-1-butyn-3-ol to the ester containing allene **2.1h**[57] (also used as a substrate) followed by reduction with $LiAlH_4$ to allenol **2.17**[57] and subsequent benzylation (Scheme 2.15).[42]



Scheme 2.15: Synthesis of substrates **2.1g** and **2.1h**

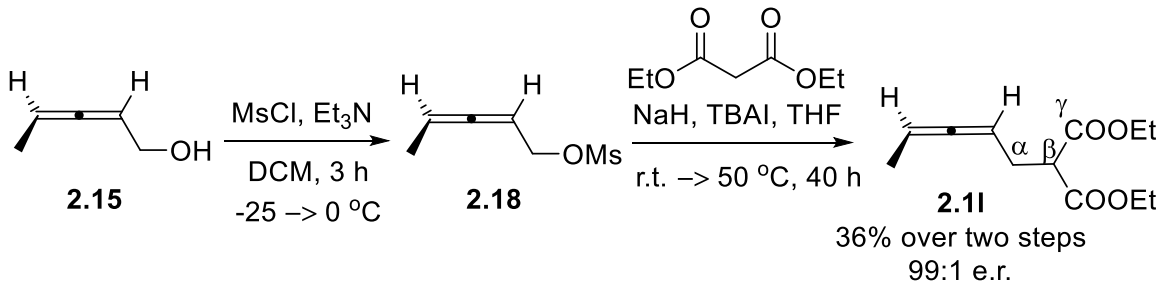
Next we targeted an allene with a different heteroatom in the β-position. It was thought that an unprotected amine or amine with a single protecting group would be likely to undergo gold-catalysed intramolecular hydroamination under our conditions,[58, 59] so a fully protected amine seemed like a more viable option. For ease of synthesis and to avoid this potential side reaction, the phthalimide protecting group was used. Allene **2.1j** was readily synthesised from the allenol **2.15** *via* the Mitsunobu reaction (Scheme 2.16).[60]



Scheme 2.16: Synthesis of substrate **2.1j**

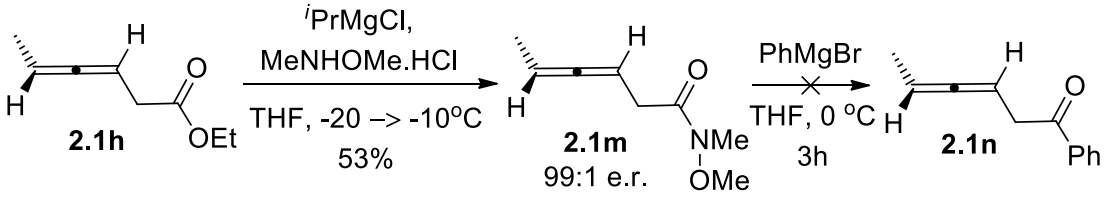
Under the same conditions, allenol **2.17** (Scheme 2.15) was also reacted with phthalimide to give allene **2.1k** in a more pleasing 96% yield.

Allene **2.1l** was synthesised by nucleophilic substitution of the mesylated allenol **2.18** with diethyl malonate (Scheme 2.17). It was chosen as a substrate in order to study the effect of not having a heteroatom at the β and γ positions.



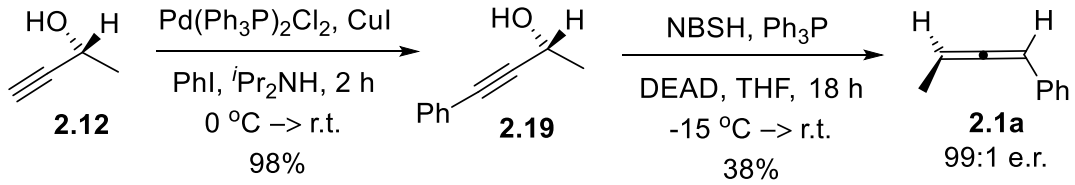
Scheme 2.17: Synthesis of substrate **2.1k**

The ester substrate **2.1h** was converted to the Weinreb amide,[61] giving substrate **2.1m**. This was initially done with the intention of converting through to the ketone **2.1n** (Scheme 2.18). However, although the ketone product **2.1n** seemed to have formed, it could not be isolated, possibly due to isomerisation of the allene into conjugation with the ketone.



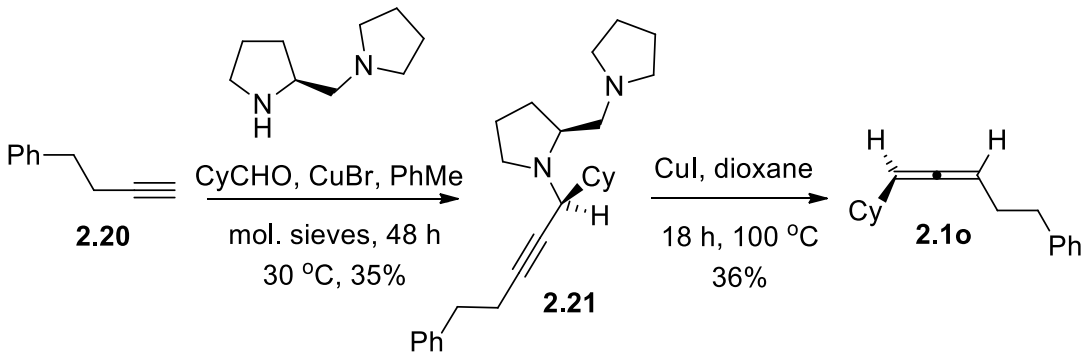
Scheme 2.18: Synthesis of substrate **2.1m**

Substrate **2.1a**, which was used by Yamamoto in his aforementioned paper on hydroalkoxylation[44] was prepared from (*R*)-1-butyn-3-ol **2.12**, by a Sonogashira coupling[62] with iodobenzene and then conversion to the allene with 2-nitrobenzenesulfonylhydrazide (NBSH) (Scheme 2.19).[63]



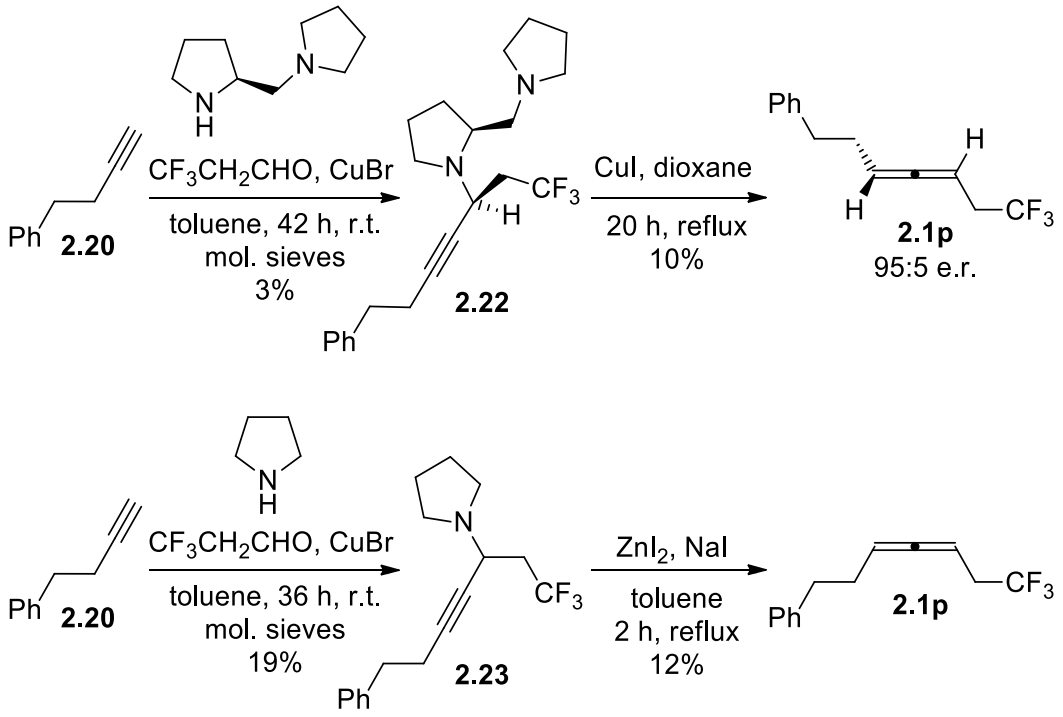
Scheme 2.19: Synthesis of substrate **2.1a**

Another route to enantioenriched 1,3-disubstituted allenes is through a Crabbé homologation. The dialkyl substituted allene **2.1o** was made in this way from 4-phenyl-1-butyne **2.20** (Scheme 2.20).[64ϖ]



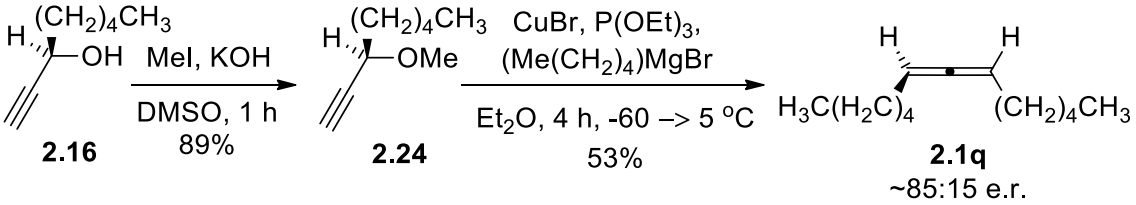
Scheme 2.20: Synthesis of substrate **2.1o**[ϖ]

The CF_3 containing allene **2.1p** or similar CF_3 containing substrates proved difficult to prepare. However, after several failed investigations, both racemic and enantioenriched allene **2.1p** were successfully prepared through a similar method to **2.1o** albeit in a low yield (Scheme 2.21).



Scheme 2.21: Synthesis of substrate **2.1p**

The final substrate discussed is the symmetrical alkyl-substituted allene **2.1q** which was synthesised through methylation of the propargylic alcohol **2.16** followed by copper-mediated S_N2' substitution (Scheme 2.22).[65]



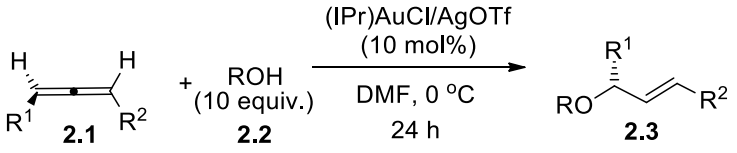
Scheme 2.22: Synthesis of substrate **2.1q**

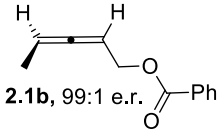
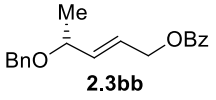
Unfortunately, allene **2.1q** could only be synthesised in approximately 85:15 e.r. which was determined by ^{1}H NMR using chiral shift reagents Eu(hfc)$_3$ and Ag(FOD).[66] This method of e.r. determination proved to be problematic due to solubility issues with Ag(FOD) and is therefore only reported as an estimation. Since allene **2.1q** is very non-polar, other more commonly used methods of e.r. determination (CSP-HPLC and CSP-GC) were unsuited to this substrate.

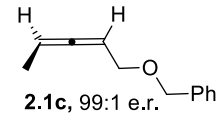
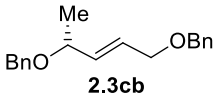
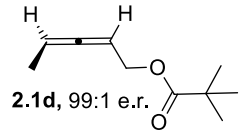
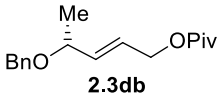
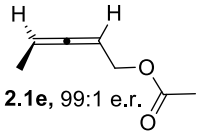
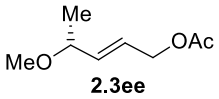
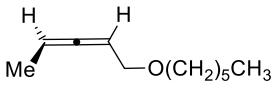
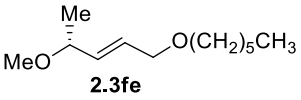
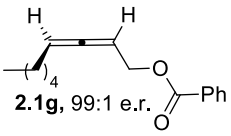
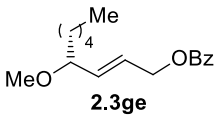
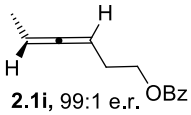
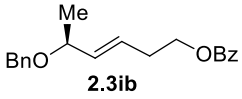
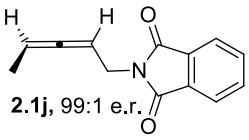
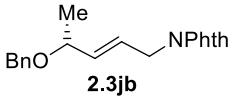
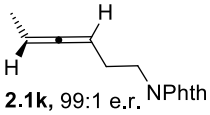
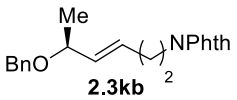
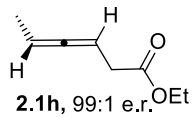
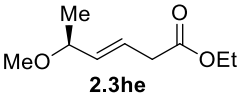
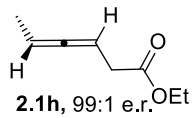
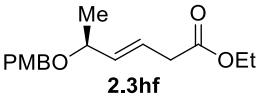
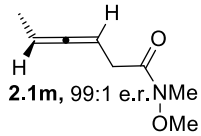
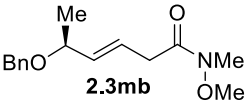
Using the strategies described above, a range of enantioenriched allenes were conveniently synthesised for use as substrates in the gold(I)-catalysed hydroalkoxylation reaction.

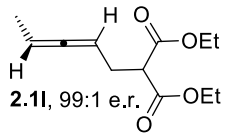
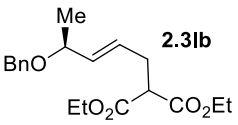
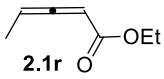
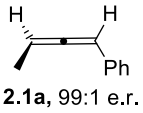
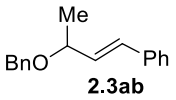
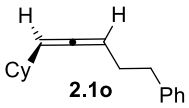
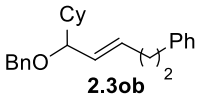
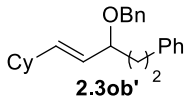
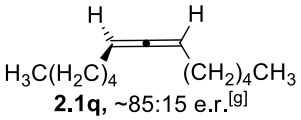
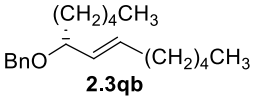
2.3.3 Allene scope

With optimised conditions and access to a range of substrates we looked to probe the scope of the gold-catalysed hydroalkoxylation reaction. In particular, we were interested in probing how much we could reduce and adapt the functionality in the allene substrate **2.1** whilst still achieving good selectivity and chirality transfer.



Entry	Allene	Alcohol	Product	Yield[a]	e.r.
1[ϖ]	 **2.1b,** 99:1 e.r.	BnOH **2.2b**	 **2.3bb**	65%	98:2[b]

2[ϖ]	 **2.1c,** 99:1 e.r.	BnOH **2.2b**	 **2.3cb**	45%	95:5[b]
3[ϖ]	 **2.1d,** 99:1 e.r.	BnOH **2.2b**	 **2.3db**	70%	93:7[c]
4[ϖ]	 **2.1e,** 99:1 e.r.	MeOH **2.2e**	 **2.3ee**	78%	94:6[c]
5[ϖ]	 **2.1f**, 99:1 e.r.	MeOH **2.2e**	 **2.3fe**	94%	87:13[d]
6[ϖ]	 **2.1g,** 99:1 e.r.	MeOH **2.2e**	 **2.3ge**	91%	97:3[b]
7	 **2.1i,** 99:1 e.r.	BnOH **2.2b**	 **2.3ib**	79%	90:10 [b]
8	 **2.1j,** 99:1 e.r.	BnOH **2.2b**	 **2.3jb**	81%	97:3[b]
9[e]	 **2.1k,** 99:1 e.r.	BnOH **2.2b**	 **2.3kb**	94%[f] 9:1 pos.	81:19[b]
10	 **2.1h,** 99:1 e.r.	MeOH **2.2e**	 **2.3he**	92%	97:3[b]
11	 **2.1h,** 99:1 e.r.	PMBOH **2.2f**	 **2.3hf**	71%	95:5[b]
12	 **2.1m,** 99:1 e.r.	BnOH **2.2b**	 **2.3mb**	58%	91:9[b]

13	 **2.1l**, 99:1 e.r.	BnOH **2.2b**	 **2.3lb**	86%	90:10[b]
14[ϖ]	 **2.1r**	BnOH **2.2b**	Mainly **2.1r** and a complex mixture of products		
15	 **2.1a**, 99:1 e.r.	BnOH **2.2b**	 **2.3ab**	79%[f] 10:1 pos.	Racemic
16[ϖ]	 **2.1o**	BnOH **2.2b**	 **2.3ob**  **2.3ob'**	71%[f] 1:0.7 pos.	-
17	 **2.1q**, ~85:15 e.r.[g]	BnOH **2.2b**	 **2.3qb**	82%	69:31[b]

[a] Isolated yields, >20:1 E:Z and positional selectivity by ^{1}H NMR unless otherwise stated**. 2.2e** was used when the product obtained using **2.2b** was not separable by CSP-HPLC, CSP-GC or chiral shift reagents. [b] Determined by CSP-HPLC [c] Determined by ^{1}H NMR using chiral shift reagent (*R*)-(-)-1-(9-anthryl)-2,2,2-trifluoroethanol [d] Determined by CSP-GC. [e] When (IPr)AuNTf$_2$ was used as catalyst instead, positional selectivity improves to >20:1; 82:18 er. [f] Combined yield. [g] Estimated by ^{1}H NMR using chiral shift reagent Eu(hfc)$_3$ and Ag(FOD), e.r. could not be definitively determined by any method attempted.

Table 2.4: Allene substrate scope

Initially, the OBz substituent **2.1b** used in our optimisation reactions was replaced with other protected alcohol groups, and to our delight it was found that removing the carbonyl (Entry 2, Table 2.4) or Ph (Entries 3-4, Table 2.4) does not significantly affect the degree of chirality transfer to the product (**2.3cb**-**2.3eb**, >93:7 e.r., Entries 2-4, Table 2.4). In order to investigate the minimum amount of functionality required to achieve good positional selectivity, the ether allene **2.1f** was investigated (Entry 5, Table 2.4). This result shows that with only an ether *O* the hydroalkoxylation reaction proceeds with perfect positional selectivity, albeit with a slightly lower degree of

chirality transfer (**2.3fe**, 87:13 e.r., Entry 5, Table 2.4). Pleasingly, swapping the Me group with a longer alkyl chain results in high yield and excellent chirality transfer (**2.3ge**, 91%, 97:3 e.r., Entry 6, Table 2.4). To our delight, moving the OBz group one CH_2 further from the allene gave only slightly reduced chirality transfer and retained >20:1 positional selectivity (**2.3bb** 98:2 Entry 1 *vs.* **2.3ib** 90:10 e.r. Entry 7, Table 2.4).

Expanding the scope to an entirely different inductively withdrawing functional group in the form of phthalimide containing allene **2.1j** proceeded very smoothly to give product **2.3jb** (81%, 97:3 e.r., Entry 8, Table 2.4). Interestingly, as before (**2.3bb** *vs.* **2.3ib**) when the functionality was placed one CH_2 further from the allene, there is a drop in the enantiomeric ratio of the product (**2.3jb** 97:3 Entry 8 *vs.* **2.3kb** 81:19 e.r. Entry 9, Table 2.4). In this example, in addition to a more substantial drop in e.r., the positional selectivity also dropped, with a 9:1 ratio of positional isomers being obtained. It should be noted however, that when the silver free catalyst (IPr)AuNTf$_2$ is used instead of the standard mixture of (IPr)AuCl and AgOTf, the positional selectivity is successfully restored to >20:1 (**2.3kb**, 82:18 e.r.). The ester allene **2.1h** was also investigated and gratifyingly gave the expected products **2.3he** and **2.3hf** in excellent yield and e.r. for both alcohols trialled (**2.3he** 92% 97:3 e.r. and **2.3hf** 72% 95:5, Entries 10-11, Table 2.4). Satisfyingly, the Weinreb amide containing substrate **2.1m** reacted well under our conditions albeit with a slight drop in yield (**2.3mb**, 58%, 91:9 e.r., Entry 12, Table 2.4). To our delight, allene **2.1l** with no heteroatoms in the β or γ position relative to the allene reacted selectivity giving one positional isomer and retaining good e.r. despite the functionality being far removed from the allene (**2.3lb**, 86%, 90:10 e.r., Entry 13, Table 2.4). Unfortunately, having the ester directly conjugated to the allene (**2.1r**) is detrimental to the reaction, presumably due to the allene being less electron-rich (Entry 14, Table 2.4).

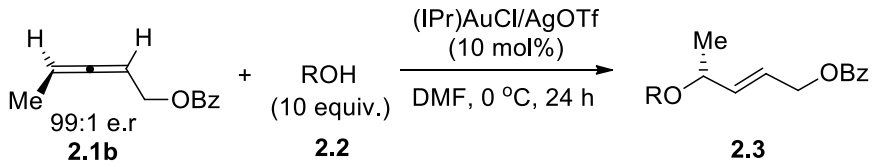
The previous examples demonstrate good positional selectivity and enantiomeric ratios with a wide range of functionalised allenes (Entries 1-13, Table 2.4). Interestingly however, with unfunctionalised allenes the reaction does not proceed with the same degree of selectivity. Aryl substituted allene **2.1a**, originally investigated by Yamamoto[44], gave a good 10:1 ratio of positional isomers. However, as reported with Yamamoto's conditions, no chirality transfer was obtained (**2.3ab**, 79%, racemic, Entry

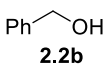
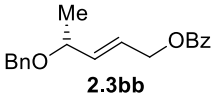
15, Table 2.4). This is likely due to the faster allene racemisation outcompeting the hydroalkoxylation for this substrate (see Section 2.3.5), as the aryl substituent can stabilise the intermediate of the allene racemisation (**1.VI**, Scheme 1.17).[41] In order to determine whether positional selectivity could be controlled by steric differentiation, the dialkyl 1,3-substituted allene **2.1o** was subjected to our conditions. Interestingly, this gave an inseparable mixture of positional isomers (**2.3ob**, 71%, 1:0.7 pos., Entry 16, Table 2.4), showing that some inductively withdrawing functionality is needed to give good positional selectivity (see Section 2.3.5). Although this limits the scope of the hydroalkoxylation to functionalised allenes, this is not necessarily a major drawback as functional group containing substrates and products are much more useful for further synthesis.

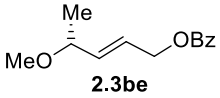
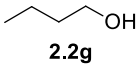
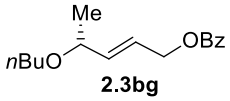
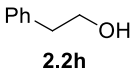
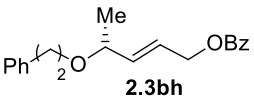
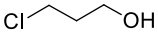
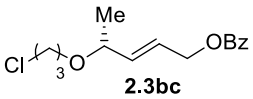
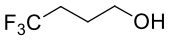
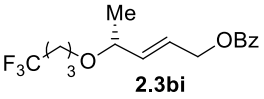
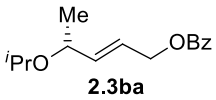
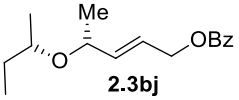
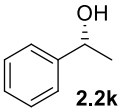
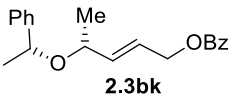
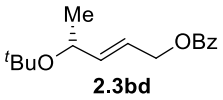
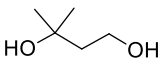
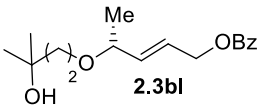
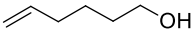
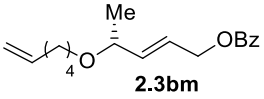
The symmetrical dialkyl substrate **2.1q** (~85:15 e.r., see Section 2.3.2) was of particular interest as positional selectivity is not an issue and if chirality transfer was to occur it would show that it is facilitated by steric interactions alone. Interestingly, some moderate chirality transfer did occur (**2.3qb**, 82%, 69:31 e.r., Entry 17, Table 2.4). However, the estimated e.r. of the starting material (see Section 2.3.2) and some loss of chirality transfer led us to refrain from drawing any major conclusions from this result.

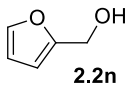
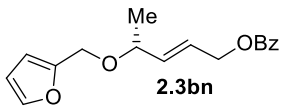
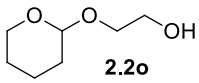
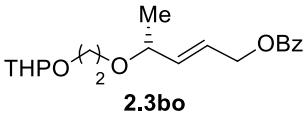
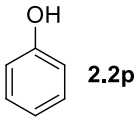
The absolute configuration was determined for products **2.3bb** and **2.3hf** (see experimental Section 2.5.5 for details) and the absolute configuration of all other products was inferred by analogy.

2.3.4 Nucleophile scope



Entry	Alcohol	Product	Yield[a]	e.r.
1	 **2.2b**	 **2.3bb**	65%	98:2[b]

2	MeOH **2.2e**	 **2.3be**	81%	>95:5[c]
3	 **2.2g**	 **2.3bg**	68%	98:2[b]
4	 **2.2h**	 **2.3bh**	62%	98:2[c]
5	 **2.2c**	 **2.3bc**	60%	97:3[b]
6	 **2.2i**	 **2.3bi**	37%	99:1[b]
7	 **2.2a**	 **2.3ba**	88%	97:3[b]
8	 **2.2j**	 **2.3bj**	78%	81:19[b]
9	 **2.2k**	 **2.3bk**	51%	97:3[b]
10	 **2.2d**	 **2.3bd**	30%	94:6[b]
11	 **2.2l**	 **2.3bl**	60%	98:2[b]
12	 **2.2m**	 **2.3bm**	66%	99:1[b]

13	 **2.2n**	 **2.3bn**	64%	99:1[b]
14	 **2.2o**	 **2.3bo**	79%	91:9[c][d]
15	 **2.2p**	-	No reaction	

[a] Isolated yields, >20:1 E:Z and positional selectivity by ^{1}H NMR analysis unless otherwise stated. [b] Determined by CSP-HPLC [c] Determined by ^{1}H NMR using chiral shift reagent (*R*)-(-)-1-(9-anthryl)-2,2,2-trifluoroethanol. [d] Determined on the THP deprotected product.

Table 2.5: Alcohol nucleophile scope[ϖ]

The alcohol nucleophile scope was investigated using allene substrate **2.1b** (Table 2.5) and gave perfect positional selectivity throughout the scope. Pleasingly, the reaction was shown to work well with a range of other primary alcohols, giving the desired allylic ethers in good yields and excellent e.r. (**2.3be**, **2.3bg**, **2.3bh**, >62%, >95:5 e.r., Entries 2-4, Table 2.5). To our delight, primary alkyl alcohols with pendent electron withdrawing Cl (**2.2c**) and CF_3 (**2.2i**) groups, also react smoothly and gave products with high e.r. albeit with a lower yield for alcohol **2.2i** (**2.3bc**, 70%, 97.3 e.r. and **2.3bi**, 37%, 99:1 e.r., Entries 5-6, Table 2.5). The more sterically hindered secondary alcohol ^{i}PrOH **2.2a** reacts well to give the desired product in good yield and e.r. (**2.3ba**, 88%, 97:3 e.r., Entry 7, Table 2.5) and homochiral secondary alcohols **2.2j** and **2.2k** also proceed with good e.r. and d.r., (**2.3bj**, 78%, 81:19 e.r. and **2.3bk**, 51%, 97:3 e.r., Entries 8-9, Table 2.5). The extremely bulky tertiary alcohol ^{t}BuOH **2.2d** reacts sluggishly under our conditions but with good chirality transfer (30%, 96:4 e.r., Entry 10, Table 2.5). Gratifyingly, this difference in reactivity allows for chemoselective reaction of diol **2.2l** at the less hindered primary end (**2.3bl**, 60%, 98:2 e.r., Entry 11, Table 2.5). Other potentially sensitive functional groups such as a pendent alkene (**2.2m**), furan (**2.2n**) or acetals (**2.2o**) are also tolerated well (**2.3bm**, **2.3bn**, **2.3bo**, >64%, >91:9 e.r., Entries 12-14, Table 2.5). However, the less nucleophilic phenol (**2.2p**) is not a viable nucleophile in this reaction (Entry 15, Table 2.5).

2.3.5 Investigation into selectivity

The allene scope revealed a great deal about why the hydroalkoxylation of enantioenriched allenes occurs with excellent selectivity. Firstly, the positional selectivity is lost when the substituents on the allene are electronically similar (**2.3ob**, 71%, 1:0.7 pos., Entry 16, Table 2.4). This is thought to be because the inductively withdrawing functional group is drawing electron density away from the carbon-carbon bond of the allene closest to it (π^2, Figure 2.1) and thereby promoting reaction at the more remote and electron-rich carbon-carbon bond (π^1, Figure 2.1).

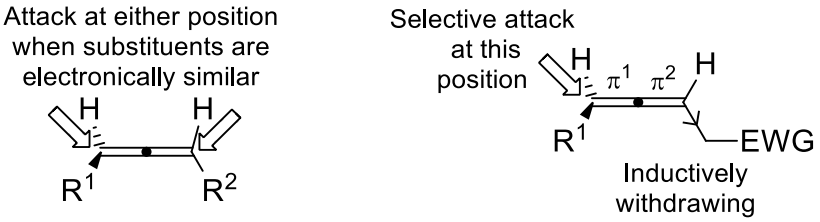
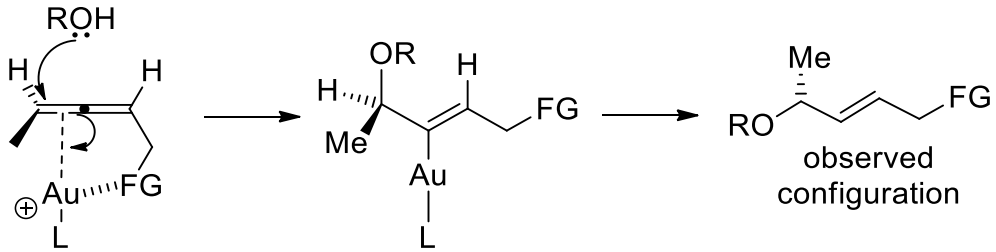


Figure 2.1: Positional selectivity through inductively withdrawing group

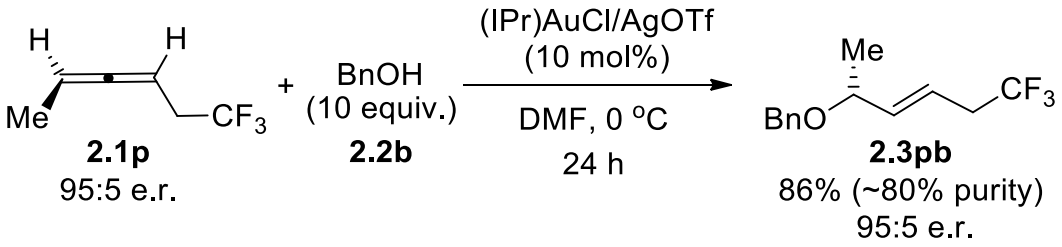
Another possible mechanism that could explain the positional selectivity observed involves the gold catalyst chelating to the functional group of the allene and so being directed towards activation of one half of the allene over the other. This mechanism would also explain the chirality transfer observed as the interaction would direct the gold to one face of the allene and through *anti* attack of the alcohol give the configuration observed (Scheme 2.23).



Scheme 2.23: Alternative selectivity through gold chelation (disproved)

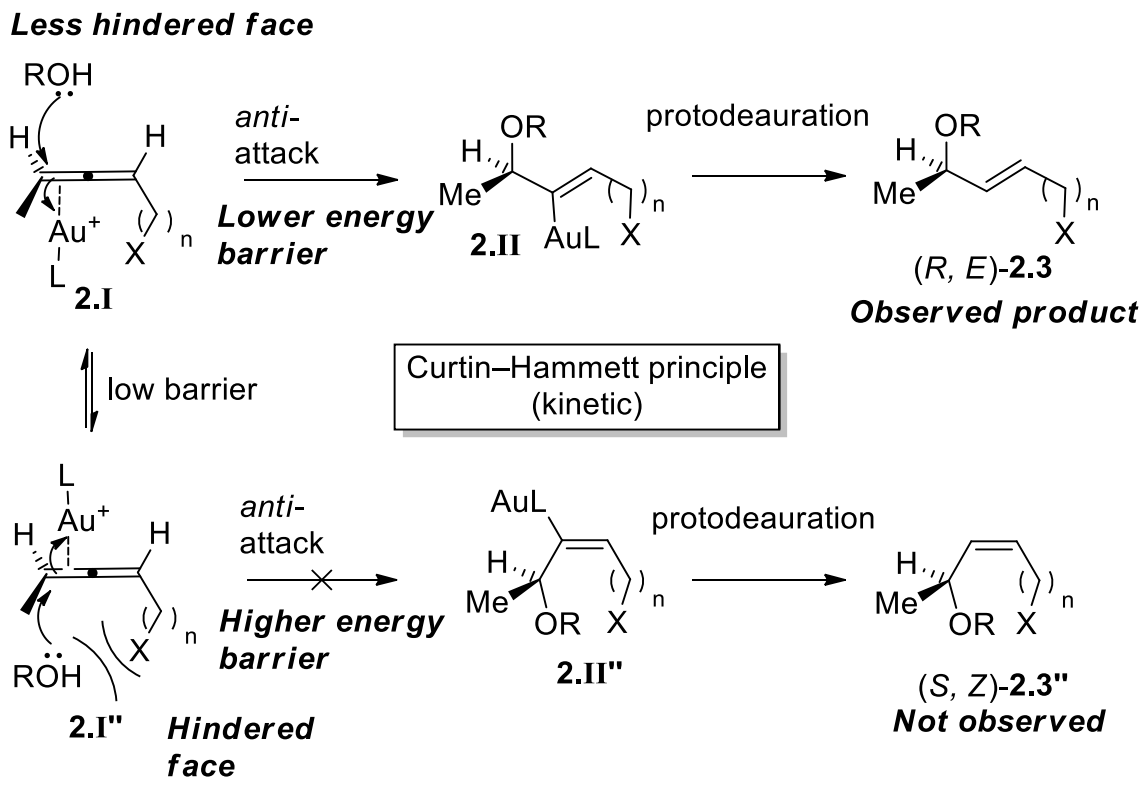
This mechanism depends entirely on the functional group being capable of chelating the gold catalyst to confer the selectivity observed. The symmetrical dialkyl allene **2.1q** was chosen as part of the scope as it has no functionality which is capable of chelating the gold catalyst. Although this substrate did suggest that some chirality transfer

occurred without the possibility of chelation (**2.3qb**, 82%, 69:31 e.r., Entry 17, Table 2.4), the result was not convincing. To investigate this further, the CF_3 containing allene **2.1p** was subjected to our conditions (Scheme 2.24). This substrate has a CF_3 group which is inductively withdrawing but does not have any functionality capable of chelating the gold catalyst.



Scheme 2.24: Gold-catalysed hydroalkoxylation of allene **2.1p**

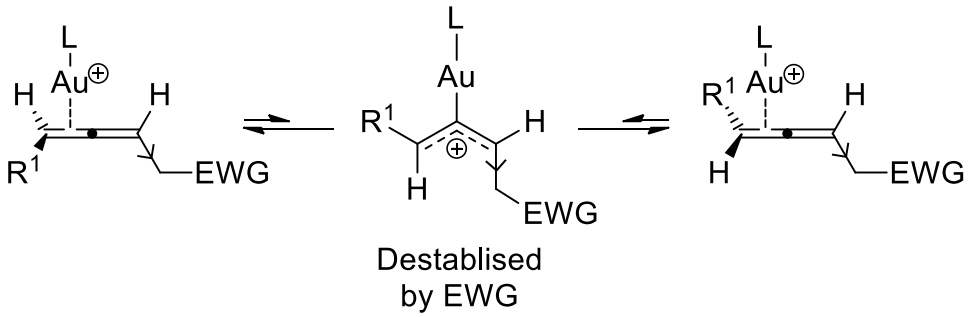
The perfect positional selectivity and chirality transfer observed for this substrate (**2.1p**) demonstrates conclusively that only an inductively withdrawing group on one substituent of the allene is required for excellent selectivity. Based on this result, the following mechanism is proposed for this reaction (Scheme 2.25).



Scheme 2.25: Proposed mechanism of selective hydroalkoxylation of allenes

It is thought that the gold catalyst can coordinate to either face of the allene and these intermediates (**2.I** and **2.I''**, Scheme 2.25) are rapidly interconverting.[67] The gold catalyst prefers to activate the more electron-rich half of the allene, which is the π-bond that is furthest from the inductively withdrawing group (see Figure 2.1). Since the face to which the gold catalyst binds is in equilibrium, in accordance with the Curtin-Hammett principle the energy barrier of the next step of the mechanism defines which product is observed. The attack of the alcohol nucleophile is preferred at the less hindered face of the allene and so, through this lower energy pathway, the observed product (*R, E*)-**2.3** is obtained after protodeauration. The product formed through attack at the lower face (*S, Z*)-**2.3''** is never detected in our reactions.

With this mechanism in mind, it follows that any loss of chirality transfer is likely due to allene racemisation (Scheme 2.26).



Scheme 2.26: Gold-catalysed 1,3-disubstituted allene racemisation

Looking back at the allene scope (Table 2.4), it can be seen that substrates which have more inductively withdrawing groups gave better chirality transfer. For example, the protected allenols which have inductively withdrawing carbonyls or benzyl groups (**2.3bb**-**2.3eb**, >93:7 e.r., Entries 1-4, Table 2.4) outperformed the less inductively withdrawing ether allene (**2.3fe**, 87:13 e.r., Entry 5, Table 2.4). Also, moving the inductively withdrawing group one CH_2 farther from the allene and so lowering its affect causes a drop in chirality transfer (**2.3bb** 98:2 Entry 1 *vs.* **2.3ib** 90:10 e.r. Entry 7 and **2.3jb** 97:3 Entry 8 *vs.* **2.3kb** 81:19 e.r., Entry 9, Table 2.4). Due to this trend of allenes with more inductively withdrawing character in one substituent outperforming those with less inductively withdrawing substituents, it was proposed that the inductively withdrawing groups destabilise the transition state of the allene racemisation mechanism (Scheme 2.26). This is thought to slow down the racemisation, thereby allowing better chirality transfer for allenes with more inductively withdrawing substituents. This would also explain why there is a drop in chirality transfer in the hydroalkoxylation of dialkyl allene **2.1q** which does not have an inductively withdrawing group (**2.3qb**, 82%, 69:31 e.r., Entry 17, Table 2.4).

Allene **2.1a** which produced totally racemic product under our conditions (**2.3ab**, 79%, racemic, Entry 15, Table 2.4) is likely quickly racemised by the gold catalyst, since having a phenyl group directly bound to the allene will stabilise the intermediate of the allene racemisation mechanism.

From this investigation, we have been able to show that having an inductively withdrawing group close to the allene ensures excellent positional selectivity by drawing electron density away from one half of the allene. The inductively

withdrawing substituent is also thought to prevent allene racemisation which, based on our proposed mechanism, is the only reason for loss of chirality transfer in the hydroalkoxylation of enantioenriched allenes.

2.4 Conclusions

The first gold(I)-catalysed hydroalkoxylation of enantioenriched 1,3-disubstituted allenes with excellent positional selectivity and chirality transfer for a range of substrates has been developed. This was achieved by developing conditions which allow the hydroalkoxylation reaction to occur whilst preventing the gold-catalysed racemisation of starting material allenes. During optimisation of the reaction it was found that the solvent, equivalents of alcohol and temperature can all be used to dampen the activity of the gold catalyst. These changes to the conditions were key in achieving excellent chirality transfer by supressing allene racemisation.

An extensive allene scope study showed that a range of substrates with one inductively withdrawing substituent proceed with perfect positional selectivity and excellent chirality transfer. This is thought to be due to the inductively withdrawing group pulling electron density away from one half of the allene and so causing selective reaction at the other, more electron-rich position of the allene. The withdrawing group also destabilises the intermediate of the allene racemisation mechanism, thereby slowing down the racemisation of these allenes and allowing for excellent chirality transfer. The allene scope study shows that a range of inductively withdrawing functional groups can be tolerated including groups with *O, N* or CF_3 in the β position, an ester or an amide. Pleasingly, when the functionality is stripped back to an ether group or the functional group is moved an extra CH_2 farther from the allene, the excellent positional selectivity is retained and there is only a slight drop in chirality transfer.

The alcohol nucleophile scope demonstrates that the reaction is tolerant to a range of primary, secondary and tertiary alcohols as well as alcohols with potentially sensitive functional groups. The yield was shown to drop with tertiary alcohols and primary alcohols with pendent electron withdrawing groups, but to our delight the chirality transfer was excellent for all the alcohol nucleophiles investigated.

2.5 Experimental

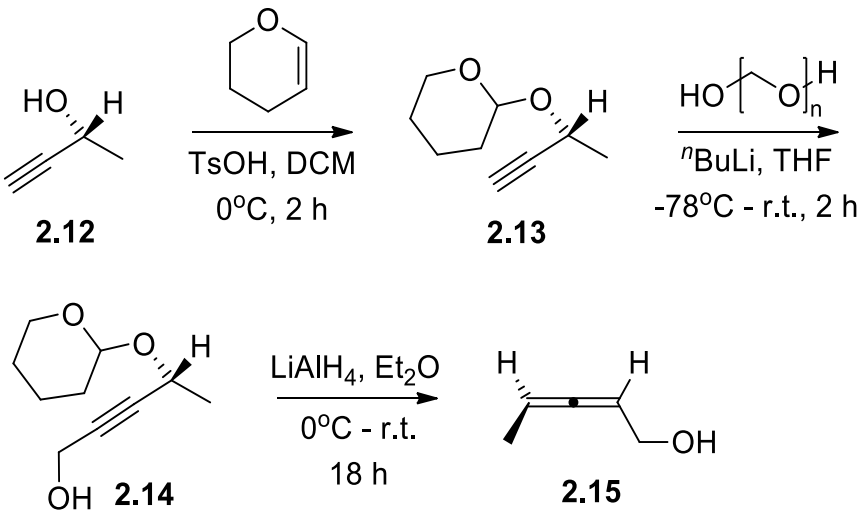
2.5.1 General considerations

^{1}H NMR spectra was recorded on Bruker AV 300 and AV 400 spectrometers at 300 and 400 MHz respectively and referenced to residual solvent. ^{13}C NMR spectra were recorded using the same spectrometers at 75 and 100 MHz respectively. Chemical shift data are quoted in parts per million (ppm) and are referenced to tetramethylsilane (TMS) or to residual solvent peaks ($CDCl_3$ at δ_H 7.26). *J* values are given in Hz and s, d, dd, dt, ddt, dtd, t, td, tt, q, qd, qt, p and m abbreviations correspond to singlet, doublet, doublet of doublet, doublet of triplet, doublet of doublet of triplet, doublet of triplet of doublet, triplet, triplet of doublet, triplet of triplet, quartet, quartet of doublet, quartet of triplet, quintet and multiplet respectively. Mass spectra were obtained at the EPSRC National Mass Spectrometry Service Centre in Swansea. Infrared spectra were obtained on Perkin-Elmer Spectrum 100 FT-IR Universal ATR Sampling Accessory, deposited neat or as a chloroform solution to a diamond/ZnSe plate. Flash column chromatography was carried out using Matrix silica gel 60 from Fisher Chemicals or Silicagel 60A from Fluorochem and TLC was performed using Merck silica gel 60 F254 pre-coated sheets and visualised by UV (254 nm) or stained by the use of aqueous acidic $KMnO_4$ or aqueous acidic ceric ammonium molybdate as appropriate. Chemicals were purchased from Sigma-Aldrich, Acros, Apollo Scientific, Fisher, Fluorochem and Manchester Organics chemical companies and used without further purification unless otherwise stated. THF, DCM and DMF were dried using an MBRAUN SPS-800 solvent purification system. Diethyl ether was purified by distilling over CaH_2. High performance liquid chromatography (HPLC) was carried out on Agilent Technologies 1120 Compact LC. Gas chromatography was carried out on a Shimadzu GC2014 with FID.

The gold(I)-catalysed reactions were carried out in screw cap 1 dram vials partially immersed in a bath of IPA cooled by a huber TC45E-F immersion chiller unless otherwise indicated. No special precautions to exclude air or moisture were taken unless otherwise indicated.

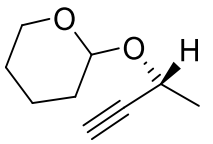
2.5.2 Preparation of allene precursors

Allenol 2.15(ϖ) – precursor for allenes **2.1b – 2.1f, 2.1j** and **2.1l**



Scheme 2.27: Synthetic route to allenol **2.15**

2-(((*R*)-But-3-yn-2-yl)oxy)tetrahydro-2*H*-pyran (2.13) (ϖ) [68]



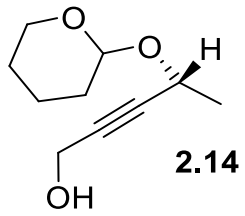
2.13

To (*R*)-1-butyn-3-ol **2.12** (3.50 g, 50.0 mmol, 1 equiv., 97% e.e.) and 3,4-dihydro-2H-pyran (5.50 mL, 60.0 mmol, 1.2 equiv.) in DCM (38 mL) at 0 °C was added TsOH (129 mg, 1.50 mol%). The solution was stirred for 2 hours at 0 °C. The reaction was diluted with DCM and quenched with a saturated solution of $NaHCO_3$, separated and then extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated. The mixture was purified by column chromatography (eluent: 20:1 to 15:1 petrol 40-60 °C/Et_2O) to yield product **2.13** as a colourless oil (6.95 g, 45.5 mmol, 91%) in a 1:0.3 mixture of diastereomers.

R_F 0.64 (15:1 petrol 40-60 °C/Et_2O); ν_{max}/cm^{-1} 3291 (C≡C-H), 2940, 2870 (C-H), 1162 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$) δ 4.93 (1H, t, *J* = 3.6 Hz, OC<u>H</u>O, major), 4.76 (1H', t, *J* = 3.3 Hz, OCHO, minor), 4.54 (1H, qd, *J* = 6.7, 2.1 Hz, $CH_3C\underline{H}$, major), 4.45 (1H', qd, *J* = 6.8, 2.1 Hz, $CH_3C\underline{H}$, minor), 4.03-3.93 (1H', m, $OCHC\underline{H}_2CH_2$, minor), 3.86-3.76 (1H, m,

OCHC<u>H</u>$_2$CH$_2$, major), 3.57-3.47 (1H + 1H', m, OCHC<u>H</u>$_2$CH$_2$, major + minor), 2.41 (1H', d, *J* = 2.2 Hz, C≡CH, minor), 2.35 (1H, d, *J* = 2.0 Hz, C≡CH, major), 1.81-1.76 (1H + 1H', m, alkyl H's, major + minor), 1.76-1.64 (1H + 1H', m, alkyl H's, major + minor), 1.64-1.49 (4H + 4H', m, alkyl H's, major + minor), 1.46 (3H, d, *J* = 6.7 Hz, C<u>H</u>$_3$CH, major), 1.43 (3H', d, *J* = 6.7 Hz, C<u>H</u>$_3$CH, minor); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 97.3 (CH, minor), 96.1 (CH, major), 84.8 (C, minor), 83.8 (C, major), 72.6 (CH, major), 72.0 (CH, minor), 62.7 (CH, major), 62.4 (CH_2, minor), 62.3 (CH_2, major), 60.7 (CH, minor), 30.7 (CH_2, minor), 30.6 (CH_2, major), 25.6 (CH_2, major), 25.5 (CH_2, minor), 22.2 (CH_3, major), 21.9 (CH_3, minor), 19.6 (CH_2, major), 19.2 (CH_2, minor).

(4*R*)-4-((Tetrahydro-2*H*-pyran-2-yl)oxy)pent-2-yn-1-ol (2.14) [ϖ][68]



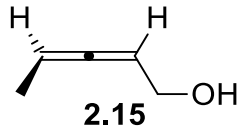
2.14

n-BuLi (17.5 mL, 2.5 M in hexanes, 43.8 mmol, 1.4 equiv.) was added dropwise (over 20 mins) to a solution of **2.13** (4.79 g, 31.3 mmol, 1.0 equiv.) in THF (105 mL) at -78 °C under Ar. Allowed to warm to room temperature and paraformaldehyde (1.89 g, 62.6 mmol, 2.0 equiv.) was added. The reaction was stirred for a further 2 hours. The reaction was diluted with Et_2O and quenched with a saturated solution of NH_4Cl and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated. The mixture was purified by column chromatography (eluent: 3:1 to 2:1 petrol 40-60 °C/EtOAc) to yield product **2.14** as a colourless oil as a 1:0.3 mixture of diastereomers (3.38 g, 18.3 mmol, 76%).

R_F 0.36 (3:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 3416 (br, OH), 2938, 2868 (C-H), 1114 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.92 (1H, t, *J* = 3.0 Hz, OC<u>H</u>O, major), 4.76 (1H', t, *J* = 3.1 Hz, minor), 4.57 (1H, qt, *J* = 6.7, 1.6 Hz, C<u>H</u>CH$_3$, major), 4.49 (1H', qt, *J* = 6.6, 1.7 Hz, C<u>H</u>CH$_3$, minor), 4.29 (2H', d, *J* = 1.6 Hz, HOC<u>H</u>$_2$, minor), 4.27 (2H, d, *J* = 1.7 Hz, HOC<u>H</u>$_2$, major), 4.02-3.93 (1H', m, OC<u>H</u>$_2$CH$_2$, minor), 3.85-3.67 (1H, m, OC<u>H</u>$_2$CH$_2$, major), 3.57-3.47 (1H + 1H', m, OC<u>H</u>$_2$CH$_2$, major + minor), 2.38 (br. 1H + 1H', m, OH, major + minor), 1.90-1.79 (1H + 1H', m, alkyl H's, major + minor), 1.77-1.65 (1H + 1H', m, alkyl H's, major + minor), 1.65-1.48 (4H + 4H', m, alkyl H's, major + minor), 1.45 (3H, d, *J* = 6.7 Hz,

CH_3, major), 1.42 (3H', d, *J* = 6.6 Hz, CH_3, minor); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 97.3 (CH, minor), 95.9 (CH, major), 86.5 (C, minor), 85.5 (C, major), 83.1 (C, major), 82.4 (C, minor), 62.7 (CH, minor), 62.6 (CH_2, major), 62.5 (CH_2, minor), 60.9 (CH, major + minor), 51.2 (CH_2, minor), 51.1 (CH_2, major), 30.7 (CH_2, minor), 30.6 (CH_2, major), 25.53 (CH_2, major), 25.46 (CH_2, minor), 22.2 (CH_3, major), 21.9 (CH_3, minor), 19.5 (CH_2, major), 19.3 (CH_2, minor).

(*S*)-Penta-2,3-dien-ol (2.15) [ϖ][68]

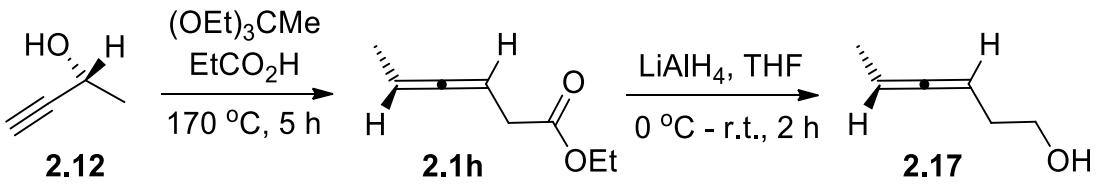


2.15

A solution of **2.14** (3.38 g, 18.3 mmol, 1.0 equiv.) in Et_2O (18 mL) was added to a solution of $LiAlH_4$ (1.26 g, 33.2 mmol, 1.8 equiv.) in Et_2O (30 mL) at 0 °C. The reaction was slowly warmed to room temperature and stirred for 18 hours. The reaction was then cooled to 0 °C and quenched by dropwise addition of 1M NaOH solution. The white suspension was filtered through celite® and washed with Et_2O and then concentrated. The mixture was purified by column chromatography (eluent: 5:1 to 2:1 pentane/Et_2O) to give product (*S*)-**2.15** as a colourless oil (1.39 g, 16.6 mmol, 49%).

R_F 0.30 (2:1 petrol 40-60 °C/Et_2O); ν_{max}/cm^{-1} 3378 (br, OH), 2938 (C-H), 1967 (C=C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 5.334-5.19 (2H, m, allene H), 4.10 (2H, dd, *J* = 5.5, 3.2 Hz, OCH_2), 1.69 (3H, dd, *J* = 6.6, 3.6 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9 (C), 91.4 (CH), 88.9 (CH), 60.8 (CH_2), 14.4 (CH_3).

Allenol 2.17 – precursor for allene **2.1i** and **2.1k**

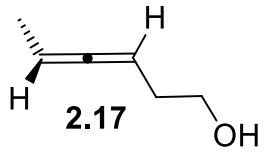


2.12 **2.1h** **2.17**

See later for experimental details for allene **2.1h**

Scheme 2.28: Synthetic route to allenol **2.17**

(*R*)-Hexa-3,4-dien-1-ol (2.17)[57]

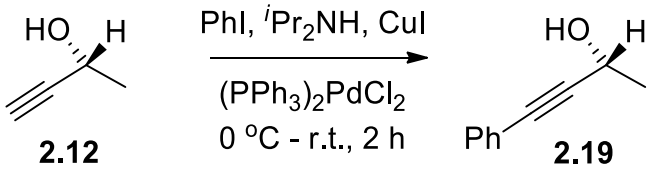


2.17

(*R*)-Ethyl hexa-3,4-dienoate **2.1h** (491 mg, 3.50 mmol, 1.0 equiv.) in dry THF (8 mL) was added dropwise to stirring solution of lithium aluminium hydride (266 mg, 7.00 mmol, 2.0 equiv.) in THF (4 mL) at 0 °C and under argon. THF (4 mL) was added and the reaction mixture was stirred at room temperature for 1 h. 1 M NaOH solution was added dropwise until the solution turned viscous and then to a clear solution with white precipitate. The reaction mixture was passed through a Celite® plug and concentrated. The mixture was purified by column chromatography (eluent: 10:1 then 6:1 hexane/EtOAc) to yield product **2.17** as a pale yellow oil (235 mg, 2.40 mmol, 69%).

R_F 0.35 (7:1 pentane/Et_2O); ν_{max}/cm^{-1} 3324 (br, OH), 2926 (C-H), 1965 (C=C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03-5.22 (2H, m, allene H), 3.73 (2H, t, OCH_2), 2.28 (2H, dtd, CH_2), 1.70 (3H, dd, $CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5 (C), 86.6 (CH), 86.2 (CH), 62.0 (CH_2), 32.2 (CH_2), 14.5 (CH_3); $[\alpha]_D^{20℃}$ = -33.6 (c = 0.66 in $CHCl_3$) [lit.[57] $[\alpha]_D^{20\,℃}$ = -93.2 (c = 1.0 in MeOH)].

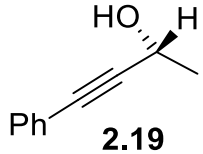
Alcohol 2.19 – precursor for allene **2.1a**



2.12 **2.19**

Scheme 2.29: Synthetic route to alcohol **2.19**

(*R*)-4-Phenylbut-3-yn-2-ol (2.19)[69]



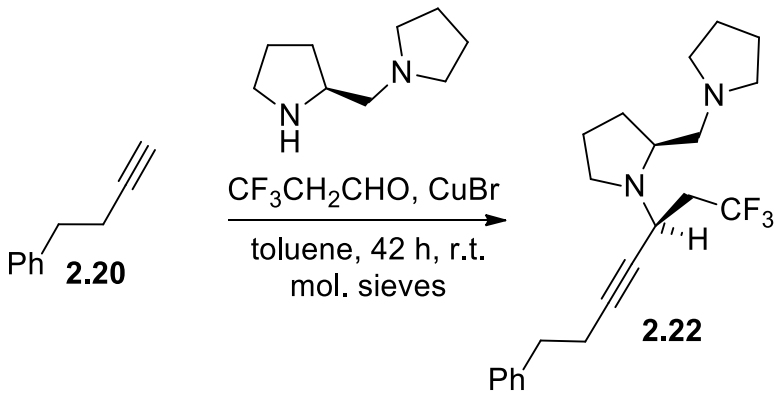
2.19

To a solution of iodobenzene (0.49 mL, 4.40 mmol, 1.1 equiv.) in diisopropylamine (5.30 mL, 38.0 mmol, 9.5 equiv.) was added bis(triphenylphosphine)palladium(II) dichloride (210 mg, 0.30 mmol, 0.70 mol%) and copper(I) iodide (195 mg, 1.03 mmol,

1.4 mol%). To the resultant mixture was added but-3-yn-2-ol **2.12** (283 mg, 4.0 mmol, 1.0 equiv.) dropwise at 0 °C. The mixture was allowed to warm to room temperature and the reaction mixture stirred for 2 h and then concentrated. The concentrated reaction mixture was loaded directly onto a silica gel column and purified by column chromatography (eluent: DCM) to yield product **2.19** as an orange oil (549 mg, 3.92 mmol, 98%).

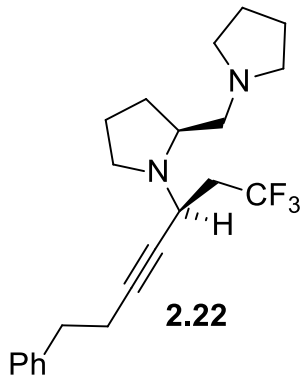
R_F 0.45 (DCM); ν_{max}/cm^{-1} 3321 (br, OH), 2981 (C-H), 1598, 1489 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.31 (5H, m, Ar-H), 4.80 (1H, qd, OCH), 2.04 (1H, br d, *J* = 4.9 Hz, OH), 1.59 (3H, d, *J* = 6.6 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.7 (CH), 128.4 (CH), 128.3 (CH), 122.6 (C), 90.9 (C), 84.0 (C), 58.9 (CH), 24.4 (CH_3); $[\alpha]_D^{20\,°C}$ = +27.2 (c = 1.03 in $CHCl_3$) [lit. $[\alpha]_D^{25\,°C}$ = +37 (c = 0.8 in $CHCl_3$)].

Alkyne 2.22 – precursor for enantioenriched allene **2.1p**



Scheme 2.30: Synthetic route to **2.22**

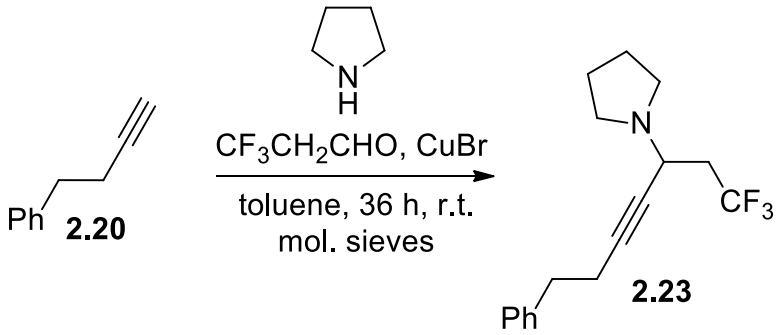
(S)-2-(Pyrrolidin-1-ylmethyl)-1-((S)-1,1,1-trifluoro-7-phenylhept-4-yn-3-yl)pyrrolidine (2.22)



Following a general procedure by Periasamy *et al.*[70] CuBr (187 mg, 20 mol%), (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine (1.00 g, 6.50 mmol, 1.0 equiv.) and dry toluene (13 ml) were added to a flask. 3,3,3-Trifluoropropanal (0.56 mL, 6.50 mmol, 1.0 equiv.), 4 Å molecular sieves (4.5 g) and 4-phenyl-1-butyne **2.20** (1.00 ml, 7.10 mmol, 1.1 equiv.) were added to the flask and stirred under N_2 at r.t. for 42 hours. The molecular sieves were removed *via* filtration and washed with Et_2O. The crude product was purified by graduated column chromatography using basic alumina (eluent 50:1 to 10:1 hexane/EtOAc) to yield product **2.22** as a yellow oil (55.0 mg, 0.17 mmol, 2.7%).

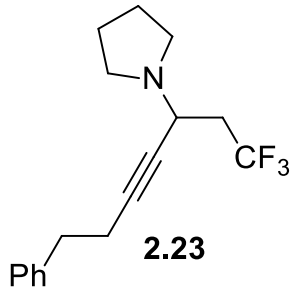
R_F 0.39 (25:1 hexane/EtOAc neutral alumina plate); ν_{max}/cm^{-1} 2960, 2787 (C-H), 1454, (C-C Ar); ^1H NMR (300 MHz, $CDCl_3$) δ 7.09-7.25 (5H, m, Ar-H), 4.20 (1H, t, *J* = 7.4 Hz, NC<u>H</u>CH_2), 2.74 (2H, t, *J* = 7.3 Hz, ≡CCH_2), 2.61-2.72 (2H, m, alkyl-H), 2.17-2.50 (11H, m, alkyl-H), 1.37-1.84 (8H, m, alkyl-H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 140.6 (C), 128.4 (CH), 128.3 (CH), 126.2 (CH), 125.8 (q, *J* = 277.3 Hz, CF_3), 85.2 (C), 61.7 (C), 59.4 (CH), 54.8 (CH_2) 47.0 (CH_2), 46.9 (q, *J* = 4.1 Hz, C<u>H</u>CH_2CF_3), 39.8 (q, *J* = 27.2 Hz, <u>C</u>H_2CF_3), 35.2 (CH_2), 30.3 (CH_2), 23.5 (CH_2), 22.9 (CH_2), 20.5 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ -64.09 (t, *J* = 10.7 Hz); Found (FTMS p NSI+) $[M + H]^+$ 379.2353 $C_{22}H_{30}F_3N_2$ requires 379.2356.

Alkyne 2.23 – precursor for racemic allene **2.1p**



Scheme 2.31: Synthetic route to **2.23**

1-(1,1,1-Trifluoro-7-phenylhept-4-yn-3-yl)pyrrolidine (2.23)

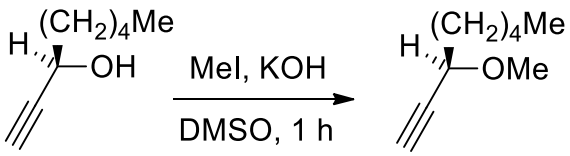


2.23

Following a general procedure by Periasamy *et al.*[70] CuBr (226 mg, 20 mol%), pyrrolidine (0.74 ml, 8.90 mmol, 1.0 equiv.) and dry toluene (14 ml) were added to a flask. 3,3,3-Trifluoropropanal (1.00 g, 8.90 mmol, 1.0 equiv.), 4 Å molecular sieves (4.5 g) and 4-phenyl-1-butyne **2.20** (1.38 ml, 9.80 mmol, 1.1 equiv.) were added to the flask and stirred under Ar at r.t. for 36 hours. The molecular sieves were removed *via* filtration and washed with Et_2O. The crude product was purified by column chromatography (eluent 30:1 then 10:1 hexane/EtOAc) to yield product **2.23** as a yellow oil (498 mg, 1.70 mmol, 19%).

R_F 0.68 (10:1 hexane/EtOAc); ν_{max}/cm^{-1} 2961 (C-H), 1496, 1455 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09-7.26 (5H, m, Ar-H), 3.78 (1H, t, *J* = 5.8 Hz, NC<u>H</u>CH_2), 2.75 (2H, t, *J* = 7.4 Hz, ≡CCH_2), 2.26-2.53 (8H, m, alkyl-H), 1.59-1.71 (4H, m, alkyl-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 140.6 (C), 128.5 (CH), 128.3 (CH), 126.2 (CH), 125.8 (q, *J* = 277.4 Hz, CF_3), 85.6 (C), 76.1 (C), 48.8 (CH_2), 48.0 (q, *J* = 3.6 Hz, C<u>H</u>CH_2CF_3), 39.7 (q, *J* = 27.3 Hz, <u>C</u>H_2CF_3), 35.1 (CH_2), 23.4 (CH_2), 20.6 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ -64.07 (t, *J* = 10.4 Hz); Found (FTMS p NSI+) $[M + H]^+$ 296.1620, $C_{17}H_{21}F_3N$ requires 296.1621.

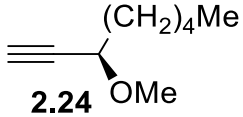
Ether 2.24 – precursor for allene **2.1q**



2.16 **2.24**

Scheme 2.32: Synthetic route to **2.24**

(*R*)-3-Methoxyoct-1-yne (2.24)[71]



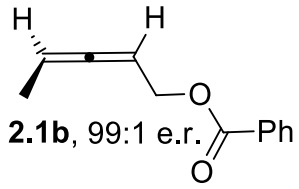
2.24

Freshly ground KOH pellets (1.14 g, 20.4 mmol, 3.4 equiv.) and iodomethane (0.75 mL, 12.0 mmol, 2 equiv.) were added to a stirring solution of (*R*)-1-octyn-3-ol **2.16** (757 mg, 6.00 mmol, 1 equiv.) in DMSO (12 mL) and stirred for 1 h. A saturated solution of $NaHCO_3$ (40 mL) and ^tBuOMe (60 mL) were added and the layers were separated. The organic layer was washed with a saturated solution of $NaHCO_3$ (30 mL) and water (30 mL) and the combined aqueous layers were extracted with ^tBuOMe (2 x 40 mL), the combined organic layers were dried over $MgSO_4$ and concentrated. The mixture was purified by column chromatography (eluent: 45:1 hexane/EtOAc) to yield product **2.24** as a thin colourless oil (745 mg, 5.33 mmol, 89%).

R_F 0.57 (40:1 hexane:EtOAc); ν_{max}/cm^{-1} 3309 (alkyne C-H), 2930 (C-H), 2360 (alkyne C-C), 1097 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$) δ 3.96 (1H, td, *J* = 6.5, 2.0 Hz, ≡CH), 3.44 (3H, s, OMe), 2.46 (1H, d, *J* = 2.1 Hz, OCH), 1.81 – 1.64 (2H, m, CH_2), 1.59 – 1.41 (2H, m, CH_2), 1.41 – 1.26 (4H, m, CH_2), 0.92 (3H, t, *J* = 6.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.8 (C), 73.6 (CH), 71.1 (CH), 56.4 (CH_3), 35.5 (CH_2), 31.5 (CH_2), 24.8 (CH_2), 22.5 (CH_2), 14.0 (CH_3).

2.5.3 Preparation of allenes

(*S*)-Penta-2,3-dien-1-yl benzoate (2.1b)[(ϖ), 68, 72]



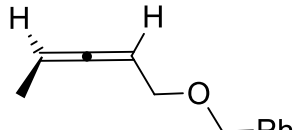
2.1b, 99:1 e.r.

To a solution of **2.15** (252 mg, 3.00 mmol, 1.0 equiv.) in DCM (12 mL) was added BzCl (697 µl, 6.00 mmol, 2.0 equiv.), pyridine (1.70 mL, 21.0 mmol, 7.0 equiv.) and 4-(dimethylamino)pyridine (73.3 mg, 0.60 mmol, 0.2 equiv.) at 0 °C. The solution was stirred for 6 hours. The reaction was quenched with 6N HCl and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The mixture was purified by column chromatography (eluent: 20:1

petrol 40-60 °C/Et_2O) to give product (*S*)-**2.1b** as a yellow oil (529 mg, 2.82 mmol, 94%, 99:1 e.r.).

R_F 0.68 (15:1 petrol 40-60 °C/Et_2O); ν_{max}/cm^{-1} 2948 (C-H), 1970 (C=C=C), 1716 (C=O), 1601, 1584, 1491,1451 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09-8.03 (2H, m, Ar-H), 7.59-7.53 (1H, m, Ar-H), 7.47-7.41 (2H, m, Ar-H), 5.40-5.30 (1H, m, allene H), 5.30-5.21 (1H, m, allene H), 4.80 (2H, dd, *J* = 6.7, 2.4 Hz, CHC$\underline{H}_2$O), 1.69 (3H, dd, *J* = 7.0, 3.2 Hz, CHC$\underline{H}_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 206.4 (C), 166.5 (C), 133.0 (CH), 130.4 (C), 129.8 (CH), 128.4 (CH), 87.9 (CH), 86.5 (CH), 63.4 (CH_2), 14.0 (CH_3); $[\alpha]_D^{22\,℃}$ = +33.6 (c = 1.07 in $CHCl_3$); CSP-GC (β-Dex, 120 °C, 35 cm s^{-1}) (*R*)-**2.1b** 73.5 min and (*S*)-**2.1b** 74.4 min.

(*S*)-((Penta-2,3-dien-1-yloxy)methyl)benzene (2.1c)[ϖ), 72]

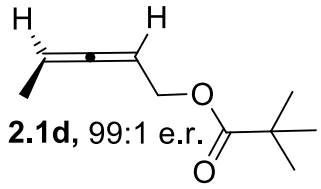


2.1c, 99:1 e.r.

Compound **2.15** (252 mg, 3.00 mmol, 1.0 equiv.) was added dropwise to a solution of NaH (60% in oil, 180 mg, 4.00 mmol, 1.5 equiv.) in THF (3.0 mL) at r.t. followed by addition of BnCl (518 µl, 4.50 mmol, 1.5 equiv.). The reaction was then stirred at 50 °C for 18 hours. The reaction was quenched with water and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated. The mixture was purified by column chromatography (eluent: 100:1 petrol 40-60 °C/EtOAc) to yield product (*S*)-**2.1c** as a yellow oil (216 mg, 1.23 mmol, 41%, 99:1 e.r.).

R_F 0.45 (80:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 3029, 2924, 2855 (C-H), 1966 (C=C=C), 1495, 1453, 1410 (C-C Ar), 1093 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.27 (5H, m, Ar-H), 5.28-5.13 (2H, m, allene-H), 4.54 (2H, s, OC$\underline{H}_2$Ph), 4.05 (2H, dd, *J* = 6.4, 2.6 Hz, CHC$\underline{H}_2$O), 1.69 (3H, dd, *J* = 6.7, 3.5 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 206.0 (C), 138.4 (C), 128.5 (CH), 128.0 (CH), 127.7 (CH), 87.9 (CH), 86.7 (CH), 71.8 (CH_2), 68.6 (CH_2), 14.3 (CH_3); $[\alpha]_D^{21\,℃}$ = +31.9 (c = 1.06 in $CHCl_3$); CSP-GC (β-Dex, 110 °C, 35 cm s^{-1}) (*R*)-**2.1c** 65.5 min and (*S*)-**2.1c** 66.1 min.

(*S*)-Penta-2,3-dien-1-yl pivalate (2.1d)[ϖ), 72]

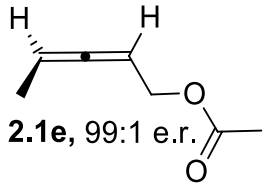


2.1d, 99:1 e.r.

Compound **2.15** (252 mg, 3.00 mmol, 1.0 equiv.) was added dropwise to a solution of NaH (60% in oil, 240 mg, 4.50 mmol, 1.5 equiv.) in THF (3.0 mL) at room temperature followed by dropwise addition of PivCl (554 µL, 6.00, 2 equiv.). The reaction was then stirred at 50 °C for 3 days. The reaction was quenched with water and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated. The mixture was purified by column chromatography (eluent: 25:1 petrol 40-60 °C /Et_2O) to yield product **2.1d** as a yellow oil (280 mg, 1.66 mmol, 55%, 99:1 e.r. (This allene could not be separated by CSP-GC or HPLC. E.r. assumed by analogy to other allenes formed by esterification of allenol **2.15**)).

R_F 0.39 (25:1 petrol 40-60 °C/Et_2O); ν_{max}/cm^{-1} 2972 (C-H), 1971 (C=C=C), 1730 (C=O), 1032 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$) δ 5.28-5.14 (2H, m, allene-H), 4.53 (2H, dd, *J* = 6.1, 3.0 Hz, C$\underline{H}_2$O), 1.67 (3H, dd, *J* = 6.7, 3.5 Hz, CH_3), 1.20 (9H, s, ^{t}Bu); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 205.9 (C), 178.4 (C), 87.9 (CH), 86.8 (CH), 62.4 (CH_2), 38.9 (C), 27.3 (CH_3), 14.1 (CH_3); Found (GC/MS EI+) $[M]^+$ 168.1152, $C_{10}H_{16}O_2$ requires 168.1150. $[\alpha]_D^{21\,°C}$ = +21.4 (c = 1.12 in $CHCl_3$).

(*S*)-Penta-2,3-dien-1-yl acetate (2.1e) [ϖ), 72]



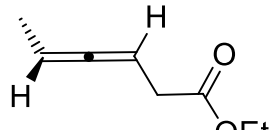
2.1e, 99:1 e.r.

Compound **2.15** (252 mg, 3.00 mmol, 1.0 equiv.) was added dropwise to a solution of NaH (60% in oil, 240 mg, 6.00 mmol, 2 equiv.) in THF (3.0 mL) at r.t. followed by dropwise addition of AcCl (427 mL, 6.00, 2 equiv.). The reaction was then stirred at 50 °C for 18 hours. The reaction was quenched with water and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated. The mixture was purified by

column chromatography (eluent: 20:1 to 10:1 petrol 40-60 °C/Et_2O) to yield product **2.1e** as a yellow oil (267 mg, 2.13 mmol, 71%, 99:1 e.r.).

R_F 0.33 (10:1 petrol 40-60 °C/Et_2O); ν_{max}/cm^{-1} 2949 (C-H), 1970 (C=C=C), 1738 (C=O), 1022 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$) δ 5.30-5.15 (2H, m, allene H), 4.57-4.52 (2H, m, OCH_2), 2.06 (3H, s, O=CCH_3), 1.71-1.56 (3H, m, CHC$\underline{H}_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 206.3 (C), 170.9 (C), 87.7 (CH), 86.4 (CH), 63.0 (CH_2), 21.1 (CH_3), 14.0 (CH_3); Found (GC/MS EI+) $[M]^+$ 126.0682, $C_7H_{10}O_2$ requires 126.0681; $[\alpha]_D^{21\,°C}$ = +45.5 (c = 1.10 in $CHCl_3$); CSP-GC (β-Dex, 100 °C, 35 cm s^{-1}) (*R*)-**2.1e** 5.7 min and (*S*)-**2.1e** 5.8 min.

(*R*)-Ethyl hexa-3,4-dienoate (2.1h)[57]

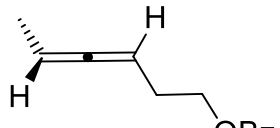


2.1h, 99:1 e.r.

(*R*)-But-3-yn-2-ol (1.23 g, 17.5 mmol, 1 equiv. 97% e.e.) and triethyl orthoacetate (10.9 mL, 59.5 mmol, 3.4 equiv.) were added to an oven dried, argon flushed round-bottom flask equipped with a Dean-Stark trap and heated to 170 °C (oil bath). Propionic acid (0.22 mL, 3.00 mmol, 0.17 equiv.) was added and the reaction mixture stirred at 170 °C. After 2.5 h, additional propionic acid (0.16 mL, 2.10 mmol, 0.21 equiv.) was added and the reaction mixture was stirred for a further 2.5 h under these conditions. After cooling to room temperature the reaction mixture was concentrated, passed through a silica plug with 10:1 hexane:EtOAc and concentrated again. The mixture was purified by column chromatography (eluent: 15:1 then 12:1 hexane/Et_2O) to yield product **2.1h** as a pale yellow oil (1.95 g, 13.8 mmol, 79%, 99:1 e.r.).

R_F 0.61 (10:1 hexane/Et_2O); ν_{max}/cm^{-1} 2981 (C-H), 1967 (C=C=C), 1734 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 5.31-5.09 (2H, m, allene H), 4.19 (2H, q, *J* = 7.1 Hz, OCH_2), 3.04 (2H, dd, CH_2), 1.69 (3H, dd, =CHC$\underline{H}_3$), 1.30 (3H, t, *J* = 7.1 Hz, $CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.8 (C), 171.7 (C), 86.8 (CH), 83.5 (CH), 60.7 (CH_2), 34.9 (CH_2), 14.2 (CH_3), 14.1 (CH_3); $[\alpha]_D^{21\,°C}$ = -27.0 (c = 1.11 in $CHCl_3$); CSP-GC (β-Dex, 90 °C, 35 cm s^{-1}) (*R*)-**2.1h** 11.6 min and (*S*)-**2.1h** 11.9 min.

(*R*)-Hexa-3,4-dien-1-yl benzoate (2.1i)[37]

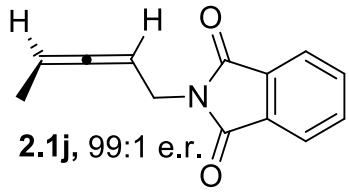


2.1i, 99:1 e.r.

To a solution of benzoyl chloride (2.94 mL, 23.1 mmol, 3.0 equiv.) in DCM (15 mL), pyridine (6.19 mL, 77.0 mmol, 10 equiv.), and 4-(dimethylamino)pyridine (281 mg, 2.31 mmol, 0.3 equiv.) were added sequentially to a solution of (R)-hexa-3,4-dien-1-ol **2.17** (745 mg, 7.70 mmol, 1.0 equiv.) in DCM (30 mL) at 0 °C. After stirring for 6 h at 0 °C the reaction was quenched by addition of 6 M HCl solution, the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 40 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated. The mixture was purified by column chromatography (eluent: 15:1 hexane/Et_2O) to yield product **2.1i** as a thin colourless oil (1.41 g, 7.01 mmol, 91%, 99:1 e.r.).

R_F 0.40 (14:1 hexane/Et_2O); ν_{max}/cm^{-1} 2953 (C-H), 1967 (C=C=C), 1716 (C=O), 1602, 1584, 1451 (C-C Ar); ^1H NMR (300 MHz, $CDCl_3$) δ 8.14-8.03 (2H, m, Ar-H), 7.65-7.41 (3H, m, Ar-H), 5.25-5.03 (2H, m, allene H), 4.42 (2H, t, OCH_2), 2.48 (2H, dtd, CH_2), 1.66 (3H, dd, $CHC\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5 (C), 166.6 (C), 132.9 (CH), 130.4 (C), 129.6 (CH), 128.3 (CH), 86.5 (CH), 86.1 (CH), 64.1 (CH_2), 28.4 (CH_2), 14.4 (CH_3); Found (FTMS p NSI+) $[M + Na]^+$ 225.0884, $C_{13}H_{14}O_2Na$ requires 225.0886; $[\alpha]_D^{21\,°C}$ = -23.1 (c = 1.04 in $CHCl_3$); CSP-GC (β-Dex, 115 °C, 35 cm s^{-1}) (*R*)-**2.1i** 145.8 min and (*S*)-**2.1i** 148.2 min.

(*S*)-2-(Penta-2,3-dien-1-yl)isoindoline-1,3-dione (2.1j)[60]



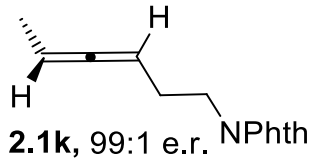
2.1j, 99:1 e.r.

Allenol **2.15** (50.5 mg, 0.60 mmol, 1 equiv.), phthalimide (132 mg, 0.90 mmol, 1.5 equiv.) and PPh_3 (236 mg, 0.90 mmol, 1.5 equiv.) in THF (4.8 mL) were stirred at 0 °C. Diisopropyl azodicarboxylate (DIAD) (0.18 mL, 0.90 mmol, 1.5 equiv.) was added dropwise and the reaction mixture was stirred for a further 1 h at 0 °C and then concentrated. The concentrated reaction mixture was loaded directly onto a silica gel

column and purified by column chromatography (eluent: 12:1 hexane/EtOAc) to yield product **2.1j** as an oily white paste (63.0 mg, 0.29 mmol, 49%, 99:1 e.r.).

R_F 0.41 (9:1 hexane/EtOAc); ν_{max}/cm^{-1} 2927 (C-H), 1968 (C=C=C), 1710 (C=O), 1612, 1466 (C-C Ar); ^1H NMR (300 MHz, $CDCl_3$) δ 7.93-7.80 (2H, m, Phth), 7.79-7.66 (2H, m, Phth), 5.25-5.10 (2H, m, allene H), 4.28 (2H, dd, CH_2), 1.58 (3H, dd, *J* = 7.6, 3.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.8 (C), 167.8 (C), 133.9 (CH), 132.2 (C), 123.2 (CH), 89.0 (C), 86.1 (C), 36.8 (CH_2), 13.9 (CH_3); Found (FTMS p NSI+) $[M + H]^+$ 214.0864, $C_{13}H_{12}NO_2$ requires 214.0863; $[\alpha]_D^{19\,℃}$ = +38.9 (c = 0.98 in $CHCl_3$); CSP-HPLC (Chiralcel OD-H, 98.2:1.8 hexane:IPA, 1 mL min^{-1}) (*R*)-**2.1j** 9.0 min and (*S*)-**2.1j** 9.6 min.

(*R*)-2-(Hexa-3,4-dien-1-yl)isoindoline-1,3-dione (2.1k)[60]

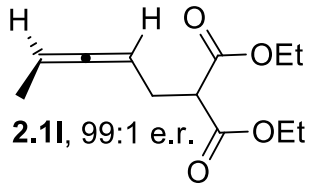


2.1k, 99:1 e.r.

Prepared in the same manner as **2.1j** from (R)-hexa-3,4-dien-1-ol **2.17** (87.4 mg, 0.90 mmol). The mixture was purified by column chromatography (eluent: 12:1 hexane/EtOAc) to give product **2.1k** as an oily white paste (196 mg, 0.86 mmol, 96%, 99:1 e.r. (This allene could not be separated by CSP-GC or HPLC. E.r. assumed by analogy to other allenes synthesised from allenol **2.17** (**2.1i**) and by the Mitsunobu reaction described (**2.1j**)).

R_F 0.41 (9:1 hexane/EtOAc); ν_{max}/cm^{-1} 2947 (C-H), 1961 (C=C=C), 1707 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.95-7.81 (2H, m, Phth), 7.80-7.67 (2H, m, Phth), 5.05 (2H, m, allene H), 3.80 (2H, t, NCH_2), 2.39 (2H, dtd, CH_2), 1.53 (3H, dd, *J* = 6.6, 3.6 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.6 (C), 168.3 (C), 133.9 (CH), 132.2 (C), 123.2 (CH), 86.5 (CH), 86.3 (CH), 37.5 (CH_2), 27.9 (CH_2), 14.3 (CH_3); Found (TOF MS) $[M+H]^+$ 228.1030, $C_{14}H_{14}NO_2$ requires 228.1024 $[\alpha]_D^{21\,℃}$ = -28.9 (c = 1.04 in $CHCl_3$).

(*S*)-Diethyl 2-(penta-2,3-dien-1-yl)malonate (2.1l)[73]



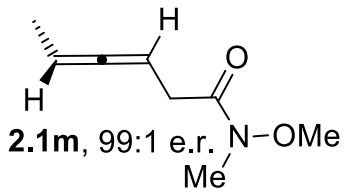
2.1l, 99:1 e.r.

To a stirring solution of allenol **2.15** (210 mg, 2.50 mmol, 1 equiv.) and triethylamine (0.54 mL, 3.88 mmol, 1.55 equiv.) in DCM (14 mL) at -25 °C mesyl chloride (0.23 mL, 3.00 mmol, 1.2 equiv.) was added dropwise over 20 minutes. The reaction mixture was warmed slowly to 0 °C and stirred for 2 ½ h. Chilled DCM (40 mL) was added and the reaction mixture washed with chilled water (30 mL), 2M HCl solution (2 x 35 mL) and a saturated solution of $NaHCO_3$ (30 mL) then dried over $MgSO_4$ and concentrated to give the crude mesylated allenol **2.18** which was used without further purification.

Diethyl malonate (0.50 mL, 3.13 mmol, 1.25 equiv.) was added to a stirring solution of NaH (60% dispersion in oil) (125 mg, 3.13 mmol, 1.25 equiv.) in THF (30 mL) at room temperature room temperature. After 30 minutes, all of the crude mesylated allenol **2.18** and tetrabutylammonium iodide (92.0 mg, 0.25 mmol, 0.1 equiv.) in THF (20 mL) was added and the reaction mixture was diluted with THF (10 mL) and stirred for 40 h at 50 °C. Diethyl ether (50 mL) was added and the solution washed with water (2 x 30 mL). The combined aqueous layers were extracted with the diethyl ether (40 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated. The mixture was purified by column chromatography (eluent: 36:1 hexane/EtOAc) to yield product **2.1l** as a colourless oil (202 mg, 0.90 mmol, 36%, 99:1 e.r.).

R_F 0.46 (15:1 pentane/Et_2O); ν_{max}/cm^{-1} 2983 (C-H), 1730 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 5.31-4.98 (2H, m, allene H), 4.30-4.13 (4H, m, OCH_2), 3.49 (1H, t, *J* = 7.5 Hz, C<u>H</u>CH_2), 2.65-2.53 (2H, m, CH_2), 1.65 (3H, dd, *J* = 9.6, 3.7 Hz, CHC<u>H</u>$_3$), 1.30 (6H, t, *J* = 7.1 Hz, CH_2C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.89 (C), 169.0 (C), 87.5 (CH), 87.0 (CH), 61.4 (CH_2), 51.6 (CH), 27.9 (CH_2), 14.3 (CH_3), 14.1 (CH_3); $[\alpha]_D^{21\,°C}$ = +34.1 (c = 0.94 in $CHCl_3$); CSP-HPLC (Chiralpak IA, 99.2:0.8 hexane:IPA, 1 mL min^{-1}) (*R*)-**2.1l** 6.9 min and (*S*)-**2.1l** 7.2 min.

(*R*)-N-Methoxy-N-methylhexa-3,4-dienamide (2.1m)[61]

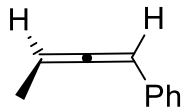


2.1m, 99:1 e.r.

2M isopropylmagnesium chloride in THF (5.25 mL, 10.5 mmol, 3 equiv.) was added dropwise over 30 minutes to a stirring solution of ester **2.1h** (491 mg, 3.50 mmol, 1 equiv.) and N,O-dimethylhydroxylamine hydrochloride (527 mg, 5.43 mmol, 1.55 equiv.) in THF (7 mL) at – 20 °C. The reaction mixture was warmed slowly to – 10 °C and stirred for a further 30 minutes. 1 M HCl solution (35 mL) was added and the organic layer separated off. The aqueous layer was extracted with EtOAc (3 x 50 mL) and the combined organic layers dried over Na_2SO_4 and concentrated. The mixture was purified by column chromatography (eluent: 4:1 hexane/EtOAc) to yield product **2.1m** as an orange oil (286 mg, 1.86 mmol, 53%, 99:1 e.r.).

R_F 0.36 (3:1 hexane/EtOAc); ν_{max}/cm^{-1} 2939 (C-H), 1659 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 5.39 – 5.22 (1H, m, allene H), 5.22 – 5.09 (1H, m, allene H), 3.72 (3H, s, OCH_3), 3.21 (3H, s, NCH_3), 3.20 – 3.14 (1H, m, CH_2), 1.68 (3H, dd, *J* = 7.0, 3.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.8 (C), 172.4 (C), 86.4 (HC), 84.1 (HC), 61.3 (CH_3), 33.0 (CH_2), 32.3 (CH_3), 14.2 (CH_3); Found (FTMS p NSI+) $[M + H]^+$ 156.1016, $C_8H_{14}NO_2$ requires 156.1019; $[\alpha]_D$ = -30.8 (c = 1.04 in $CHCl_3$); CSP-GC (β-Dex, 100 °C, 35 cm s^{-1}) (*R*)-**2.1m** 39.8 min and (*S*)-**2.1m** 40.4 min.

(*S*)-Buta-1,2-dien-1-ylbenzene (2.1a)[74]



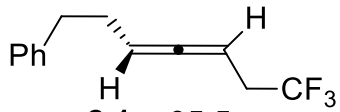
2.1a, 99:1 e.r.

Diethyl azodicarboxylate (DEAD) (0.70 mL, 4.42 mmol, 1.3 equiv.) was added to a solution of PPh_3 (1.15 g, 4.42 mmol, 1.3 equiv.) in THF (13 mL) at -15 °C. After 10 min, a solution of (R)-4-phenylbut-3-yn-2-ol **2.19** (497 mg, 3.40 mmol, 1 equiv.) in THF (10 mL) was added to the yellow reaction mixture, followed 10 min later by a solution of 2-nitrobenzenesulfonylhydrazide (NBSH) (1.04 g, 4.76 mmol, 1.4 equiv.) in THF (13 mL). The resulting suspension was held at -15 °C for 1 h, warmed to room temperature and

left to stand overnight and then concentrated. The concentrated reaction mixture was loaded directly onto a silica gel column and purified by column chromatography (eluent: hexane) to yield product **2.1a** as an orange oil (168 mg, 1.29 mmol, 38%, 99:1 e.r.).

R_F 0.74 (hexane); ν_{max}/cm^{-1} 3028, 2982, 2920 (C-H), 1946 (C=C=C), 1598, 1496, 1463 (C-C Ar); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.15 (5H, m, Ar-H), 6.13 (1H, dq, *J* = 6.4, 3.2 Hz, allene H), 5.57 (1H, p, *J* = 7.0 Hz, allene CH), 1.82 (3H, dd, *J* = 7.1, 3.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0 (C), 135.1 (C), 128.5 (CH), 126.6 (CH), 94.0 (CH), 89.6 (CH), 14.1 (CH_3); $[\alpha]_D^{21℃}$ = -32.7 (c = 0.98 in $CHCl_3$) [lit.[75] $[\alpha]_D^{20\,℃}$ = -238 (c = 1.33 in acetone)]; CSP-GC (β-Dex, 93 °C, 35 cm s^{-1}) (*R*)-**2.1a** 20.4 min and (*S*)-**2.1a** 20.8 min.

(*R*)-(7,7,7-Trifluoro-4l5-hepta-3,4-dien-1-yl)benzene (2.1p)

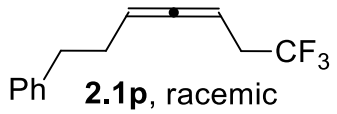


2.1p, 95:5 e.r.

Following a general procedure by Periasamy *et al.*[70] compound **2.22** (93.0 mg, 0.30 mmol, 1.0 equiv.), dry dioxane (1.2 ml) and CuI (29.2 mg, 0.15 mmol, 0.5 equiv.) was added to a flask and refluxed for 20 hours. The crude product was purified by column chromatography (eluent: petrol 40-60 °C) to yield product **2.1p** as a yellow oil (7.0 mg, 0.03 mmol, 10%, 95:5 e.r).

R_F 0.45 (hexane); ν_{max}/cm^{-1} 3028, 2927, 2858 (C-H), 1969 (C=C=C), 1496, 1454 (C-C Ar); ^1H NMR (300 MHz, $CDCl_3$) δ 7.18-7.28 (2H, m, Ar-H), 7.05-7.17 (3H, m, Ar-H), 5.13-5.28 (1H, m, Allene-H), 4.89-5.05 (1H, m, Allene-H), 2.49-2.77 (4H, m, alkyl-H), 2.16-2.37 (2H, m, alkyl-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 207.0 (C), 141.4 (C), 128.5 (CH), 128.3 (CH), 126.0 (CH), 125.9 (q, *J* = 276.9 Hz, CF_3), 91.8 (CH), 80.9 (q, *J* = 4.3 Hz, C<u>H</u>CH_2CF_3), 35.0 (CH_2), 34.5 (q, *J* = 29.7 Hz, <u>C</u>H_2CF_3), 29.9 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ -66.93 (t, *J* = 10.8 Hz); Found (TOF MS ASAP+) $[M + H]^+$ 227.1049, $C_{13}H_{14}F_3$ requires 227.1048; $[\alpha]_D^{21℃}$ = -12.0 (c = 0.5 in $CHCl_3$); CSP-GC (β-Dex, 135 °C, 35 cm s^{-1}) (*R*)-**2.1p** 12.5 min and (*S*)-**2.1p** 12.8 min.

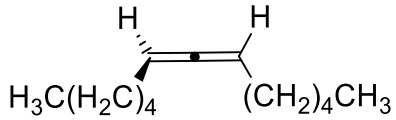
(7,7,7-Trifluoro-4l5-hepta-3,4-dien-1-yl)benzene (2.1p)[70]



2.1p, racemic

Following a general procedure by Periasamy *et al.*[70] ZnI_2 (265 mg, 0.83 mmol, 0.5 equiv.) and NaI (136 mg, 0.91 mmol, 0.55 equiv.) were added to a flask and dried by heating under vacuum. The flask was flushed with argon and a solution of compound **2.23** (488 mg, 1.70 mmol, 1 equiv.) in toluene (8 mL) was added. The solution was refluxed for 2 hours, allowed to cool to r.t. and passed through a silica plug with Et_2O. The crude product was purified by column chromatography (eluent: petrol 40-60 ^oC) to yield product **2.1p** as a colourless oil (45 mg, 0.20 mmol, 12%). See above for characterisation.

(*S*)-Trideca-6,7-diene (2.1q)[65]



2.1q, ~85:15 e.r.

A solution of copper(I) bromide (912 mg, 6.36 mmol, 1.2 equiv.) and triethyl phosphite (2.18 mL, 12.7 mmol, 1.2 equiv.) in diethyl ether (6.4 mL) was added to diethyl ether (30 mL) at -40 °C. 2 M pentylmagnesium bromide in diethyl ether (3.18 mL, 6.36 mmol, 1.2 equiv.) was added dropwise giving a yellow precipitate and the reaction mixture was stirred at -30 °C for 30 min then cooled to -60 °C before dropwise addition of 3-methoxyoct-1-yne **2.24** (745 mg, 5.30 mmol, 1.0 equiv.) in diethyl ether (9 mL). The reaction mixture was stirred at -40 °C for 90 minutes and then allowed to warm to 5 °C over a further 90 minutes. The solution was washed with aqueous solution (1 part aqueous ammonia 4 parts sat. aqueous ammonium chloride) (50 mL). The aqueous layer was extracted with diethyl ether (2 x 50ml) and the combined organic layers were washed with aqueous solution (3 x 50 mL), dried over $MgSO_4$ and carefully concentrated. The mixture was purified by column chromatography (eluent: pentane) to yield product **2.1q** as a thin colourless oil (507 mg, 2.81 mmol, 53%, 85:15 e.r.).

R_F 0.91 (pentane); ν_{max}/cm^{-1} 2957, 2924, 2872, 2855 (C-H), 1962 (C=C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 5.09 (2H, dt, *J* = 9.7, 5.3 Hz, allene H), 2.07 – 1.95 (4H, m, CH_2), 1.52

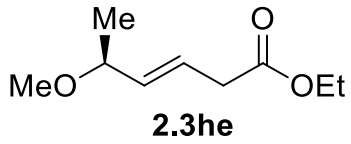
– 1.24 (12H, m, CH_2), 1.05 – 0.85 (6H, m, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9 (C), 90.9 (CH), 31.6 (CH_2), 29.5 (CH_2), 29.0 (CH_2), 22.6 (CH_2), 14.1 (CH_3); $[\alpha]_D$ = +69.2 (c = 0.014 in $CHCl_3$); e.r. could not be accurately determined due to solubility issues but was estimated by ^1H NMR with AgFOD and $Eu(hfc)_3$ as chiral shift reagents.[66]

2.5.4 Gold-catalysed hydroalkoxylation reactions

General procedure

Allene **2.1** (0.14 mmol, 1.0 equiv.), alcohol nucleophile **2.2** (1.40 mmol, 10 equiv.) and DMF (0.14 mL) were added to a vial and stirred at 0 °C. IPrAuCl (8.7 mg, 10 mol%) was added followed by AgOTf (3.6 mg, 10 mol%). The reaction was stirred at 0 °C for 24 h. The crude product was then passed through two silica plugs and washed with Et_2O. The solution was washed with water and brine and the organic layer was dried over $MgSO_4$, then concentrated. The crude mixture was purified by column chromatography to yield product **2.3**.

(*S,E*)-Ethyl 5-methoxyhex-3-enoate (2.3he)

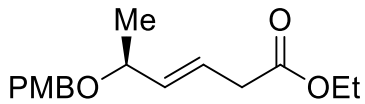


2.3he

General procedure followed and crude purified by column chromatography (eluent 10:1 hexane/EtOAc) to yield product **2.3he** as a colourless oil (23.9 mg, 0.13 mmol, 92%, 97:3 e.r.).

R_F 0.22 (10:1 hexane/EtOAc); ν_{max}/cm^{-1} 2978, 2932, 2820 (C-H), 1735 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 5.77 (1H, dtd, *J* = 15.3, 6.9, 0.6 Hz, =C<u>H</u>CH_2), 5.49 (1H, ddt, *J* = 15.5, 7.6, 1.4 Hz, =C<u>H</u>CHO), 4.18 (2H, q, *J* = 7.1 Hz, OCH_2), 3.75 (1H, p, *J* = 6.6 Hz, CHO), 3.29 (3H, s, OCH_3), 3.11 (2H, d, *J* = 6.9 Hz, CH_2), 1.29 (3H, t, *J* = 7.1 Hz, CH_2CH_3), 1.29 (3H, d, *J* = 6.4 Hz, $OCHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6 (C), 135.7 (CH), 124.3 (CH), 77.5 (CH), 60.7 (CH_2), 55.9 (CH_3), 37.7 (CH_2), 21.1 (CH_3), 14.2 (CH_3); Found (FTMS p NSI+) $[M + NH_4]^+$ 190.1436, $C_9H_{20}O_3N$ 190.1436; $[\alpha]_D$ = -26.0 (c = 1.00 in $CHCl_3$); CSP-HPLC (Chiralpak IC, 99.3:0.7 hexane:IPA, 1 mL min^{-1}) (*R*)-**2.3he** 13.0 min and (*S*)-**2.3he** 15.0 min.

(*S,E*)-Ethyl 5-((4-methoxybenzyl)oxy)hex-3-enoate (2.3hf)

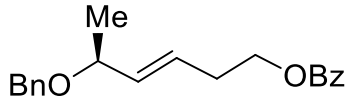


2.3hf

General procedure followed and crude purified by column chromatography (eluent 9:1 hexane/EtOAc) to yield product **2.3hf** as a colourless oil (27.7 mg, 0.10 mmol, 71%, 95:5 e.r.).

R_F 0.31 (9:1 hexane/EtOAc) ν_{max}/cm^{-1} 2976 (C-H), 1732 (C=O), 1578, 1512, 1464 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.23 (2H, m, Ar-H), 6.96 – 6.84 (2H, m, Ar-H), 5.78 (1H, dtd, *J* = 15.4, 6.9, 0.6 Hz, =C<u>H</u>CH_2), 5.56 (1H, ddt, *J* = 15.5, 7.6, 1.3 Hz, =C<u>H</u>CH), 4.52 (1H, d, *J* = 11.5 Hz, ArOCHH), 4.35 (1H, d, *J* = 11.5 Hz, ArOCHH), 4.19 (2H, q, *J* = 7.1 Hz, C<u>H</u>$_2$$CH_3$), 3.95 (1H, p, *J* = 7.1 Hz, OCH), 3.83 (3H, s, OCH_3), 3.13 (2H, dt, *J* = 6.8, 1.6 Hz, C<u>H</u>$_2$CH), 1.30 (3H, t, *J* = 7.1 Hz, CH_2C<u>H</u>$_3$), 1.29 (3H, d, *J* = 6.4 Hz, CHC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6 (C), 159.1 (C), 136.0 (CH), 130.8 (C), 129.3 (CH), 124.3 (CH), 113.8 (CH), 74.9 (CH), 69.5 (CH_2), 60.7 (CH_2), 55.3 (CH_3), 37.7 (CH_2), 21.5 (CH_3), 14.2 (CH_3); $[\alpha]_D$ = -34.4 (c = 0.99 in $CHCl_3$); CSP-HPLC (Chiralpak IC, 95:5 hexane:IPA, 1 mL min^{-1}) (*R*)-**2.3hf** 9.7 min and (*S*)-**2.3hf** 10.4 min.

(*S, E*)-5-(Benzyloxy)hex-3-en-1-yl benzoate (2.3ib)



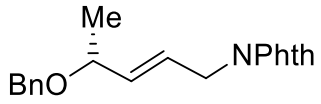
2.3ib

General procedure followed and crude purified by column chromatography (eluent 7:1 hexane/Et_2O) to yield product **2.3ib** as a colourless oil (36.3 mg, 0.11 mmol, 79%, 90:10 e.r.).

R_F 0.17 (8:1 hexane:Et_2O); ν_{max}/cm^{-1} 2972, 2861 (C-H), 1716 (C=O), 1602, 1584, 1494, 1452 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03-8.11 (2H, m, Ar-H), 7.53-7.62 (1H, m, Ar-H), 7.18-7.52 (2H, m, Ar-H), 7.23-7.39 (5H, m, Ar-H), 5.72 (1H, dt, *J* = 16.0, 6.5 Hz, CH_2<u>H</u>C=), 5.60 (1H, dd, *J* = 16.0, 8.0 Hz, OCH<u>H</u>C=), 4.56 (1H, d, *J* = 12.0 Hz, PhCH_2O), 4.43 (2H, t, *J* = 6.5, BzOCH_2), 4.38 (1H, d, *J* = 12.0 Hz, PhCH_2O), 3.87-4.02 (1H, m, OCH), 2.59 (2H, q, *J* = 6.5 Hz, CH_2), 1.30 (3H, d, *J* = 6.4 Hz, CHC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ

166.53 (C), 138.8 (C), 135.1 (CH), 132.9 (CH), 130.3 (C), 129.6 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 127.6 (CH), 127.4 (CH), 75.6 (CH), 69.8 (CH_2), 64.0 (CH_2), 31.8 (CH_2), 21.7 (CH_3); Found (FTMS p NSI+) $[M + NH_4]^+$ 328.1910, $C_{20}H_{26}O_3N$ requires 328.1907; $[\alpha]_D$ = -19.1 (c = 0.84 in $CHCl_3$); CSP-HPLC (Chiralpak IA, 99.5:0.5 hexane:IPA, 1 mL min^{-1}) (*R*)-**2.3ib** 10.9 min and (*S*)-**2.3ib** 11.4 min.

(*R,E*)-2-(4-(Benzyloxy)pent-2-en-1-yl)isoindoline-1,3-dione (2.3jb)

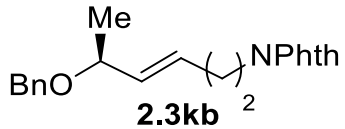


2.3jb

General procedure followed and crude purified by column chromatography (eluent 9:1 hexane/EtOAc) to yield product **2.3jb** as a colourless oil (39.2 mg, 0.11 mmol, 81%, 97:3 e.r.).

R_F 0.41 (6:1 hexane/EtOAc); ν_{max}/cm^{-1} 2973, 2863 (C-H), 1709 (C=O), 1614, 1467, 1453 (C-C Ar); ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 – 7.83 (2H, m, Phth-H), 7.82 – 7.68 (2H, m, Phth-H), 7.44 – 7.20 (5H, m, Ar-H), 5.83 – 5.62 (2H, m, alkene H), 4.55 (1H, d, *J* = 11.9 Hz, $PhOCH_2$), 4.38 (1H, d, *J* = 11.9 Hz, $PhOCH_2$), 4.36 – 4.30 (2H, m, NCH_2), 3.96 (1H, p, *J* = 6.3 Hz, OCH), 1.29 (3H, d, *J* = 6.4 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9 (C), 138.6 (C), 135.7 (CH), 134.0 (CH), 132.1 (C), 128.3 (CH), 127.7 (CH), 127.4 (CH), 125.2 (CH), 123.3 (CH), 74.9 (CH), 70.1 (CH_2), 39.0 (CH_2), 21.4 (CH_3); Found (FTMS p NSI+) $[M + NH_4]^+$ 346.2743, $C_{22}H_{36}O_2N$ requires 346.2741; $[\alpha]_D$ = -24.0 (c = 1.00 in $CHCl_3$); CSP-HPLC (Chiralpak IC, 98.3:1.7 hexane:IPA, 1 mL min^{-1}) (*R*)-**2.3jb** 20.5 min and (*S*)-**2.3jb** 22.1 min.

(*S,E*)-2-(5-(Benzyloxy)hex-3-en-1-yl)isoindoline-1,3-dione (2.3kb)

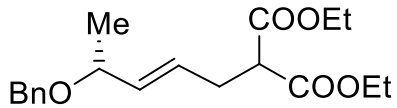


2.3kb

General procedure followed and crude purified by column chromatography (eluent 9:1 hexane/EtOAc) to yield an inseparable mixture of products **2.3kb** and **2.3kb'** as a colourless oil (46.5 mg, 0.13 mmol, 94%, 81:19 e.r., 9:1 positional isomers).

R_F 0.25 (9:1 hexane/EtOAc); ν_{max}/cm^{-1} 2928 (C-H), 1708 (C=O), 1615, 1465, 1495, 1467 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 – 7.75 (2H, m, Phth-H), 7.75 – 7.55 (2H, m, Phth-H), 7.42 – 7.15 (5H, m, Ar-H), 5.64 (1H, dt, *J* = 15.4, 7.0 Hz, $CH_2\underline{H}C$=), 5.45 (1H, dd, *J* = 15.4, 7.7 Hz, $OCH\underline{H}C$=), 4.41 (1H, d, *J* = 11.9 Hz, PhOCHH), 4.26 (1H, d, *J* = 11.9 Hz, PhOCHH), 3.97 – 3.68 (3H, m, OCH + NCH_2), 2.60 – 2.42 (2H, m, CH_2), 1.18 (3H, d, *J* = 6.4 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3 (C), 138.8 (C), 135.4 (CH), 133.9 (CH), 132.0 (C), 128.4 (CH), 128.3 (CH), 127.6 (CH), 127.3 (CH), 123.2 (CH), 75.4 (CH), 69.7 (CH_2), 37.4 (CH_2), 31.4 (CH_2), 21.5 (CH_3); $[\alpha]_D$ = -21.9 (c = 1.28 in $CHCl_3$); Found (FTMS p NSI+) $[M + NH_4]^+$ 353.1857, $C_{21}H_{25}N_2O_3$ requires 353.1860; CSP-HPLC (Chiralpak IC, 98.3:1.7 hexane:IPA, 1 mL min^{-1}) (*R*)-**2.3kb** 14.7 min and (*S*)-**2.3kb** 16.7 min.

(*R,E*)-Diethyl 2-(4-(benzyloxy)pent-2-en-1-yl)malonate (2.3lb)

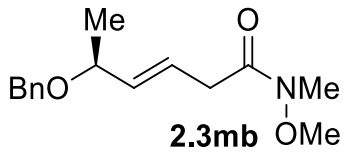


2.3lb

General procedure followed and crude purified by column chromatography (eluent 12:1 hexane/EtOAc) to yield product **2.3lb** as a colourless oil (42.5 mg, 0.12 mmol, 86%, 90:10 e.r.).

R_F 0.24 (10:1 hexane:EtOAc); ν_{max}/cm^{-1} 2980, 2931 (C-H), 1730 (C=O), 1496, 1454 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.19 (5H, m, Ar-H), 5.64 (1H, dt, *J* = 15.4, 6.4 Hz, =$C\underline{H}CH_2$), 5.54 (1H, dd, *J* = 15.5, 7.2 Hz, =$C\underline{H}CH$), 4.55 (1H, d, *J* = 11.9 Hz, OCH_2), 4.36 (1H, d, *J* = 11.9 Hz, OCH_2), 4.22 (4H, m, $OC\underline{H_2}CH_3$), 3.90 (1H, app. p, *J* = 6.4 Hz, OCH), 3.46 (1H, t, *J* = 7.5 Hz, $C\underline{H}CH_2$), 2.69 (2H, t, *J* = 6.9 Hz, =$CHC\underline{H_2}$), 1.35 – 1.23 (9H, m, $CH_2C\underline{H_3}$ + $CHC\underline{H_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9 (C), 138.8 (C), 135.2 (CH), 128.3 (CH), 128.0 (CH), 127.7 (CH), 127.4 (CH), 75.3 (CH), 69.7 (CH_2), 61.4 (CH_2) , 52.0 (CH), 31.4 (CH_2), 21.6 (CH_3), 14.1 (CH_3); Found (FTMS p NSI+) $[M + NH_4]^+$ 352.2122, $C_{19}H_{30}O_5N$ requires 352.2118; $[\alpha]_D$ = +29.1 (c = 1.17 in $CHCl_3$); CSP-HPLC (Chiralpak IC, 98:2 hexane:IPA, 1 mL min^{-1}) (*R*)-**2.3lb** 13.1 min and (*S*)-**2.3lb** 14.3 min.

(*S,E*)-5-(Benzyloxy)-N-methoxy-N-methylhex-3-enamide (2.3mb)

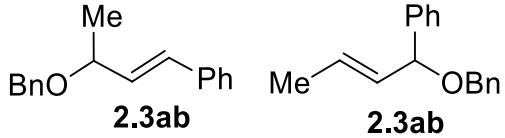


2.3mb

General procedure followed and crude purified by column chromatography (eluent 4:1 then 3:1 hexane/EtOAc) to yield product **2.3mb** as a colourless oil (21.6 mg, 0.08 mmol, 58%, 91:9 e.r.).

ν_{max}/cm^{-1} 2971, 2932, 2865 (C-H), 1660 (C=O), 1495, 1453 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 – 7.13 (5H, m, Ar-H), 5.85 (1H, dt, *J* = 15.0, 6.8 Hz, $CH_2\underline{H}C$=), 5.57 (1H, ddt, *J* = 15.5, 7.7, 1.4 Hz, OC$\underline{H}$HC=), 4.59 (1H, d, *J* = 11.9 Hz, PhOCHH), 4.42 (1H, d, *J* = 11.9 Hz, PhOCHH), 3.98 (1H, p, *J* = 6.8 Hz, OCH), 3.73 (3H, s, OCH_3), 3.28 (2H, d, *J* = 6.7 Hz, CH_2), 3.23 (3H, s, NCH_3), 1.32 (1H, d, *J* = 6.4 Hz, OCHC$\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4 (C), 138.8 (C), 135.5 (CH), 128.3 (CH), 127.7 (CH), 127.4 (CH), 125.3 (CH), 75.4 (CH), 69.8 (CH_2), 61.3 (CH_3), 35.6 (CH_2), 32.3 (CH_3), 21.5 (CH_3); Found (FTMS p NSI+) [M + NH_4]$^+$ 264.1592, $C_{15}H_{22}O_3N$ requires 264.1594; $[\alpha]_D$ = -34.7 (c = 1.21 in $CHCl_3$); CSP-HPLC (Chiralpak IC, 95:5 hexane:IPA, 1 mL min^{-1}) (*R*)-**2.3mb** 25.7 min and (*S*)-**2.3mb** 30.9 min.

(*E*)-(3-(Benzyloxy)but-1-en-1-yl)benzene (2.3ab) + (E)-(1-(benzyloxy)but-2-en-1-yl)benzene (2.3ab')



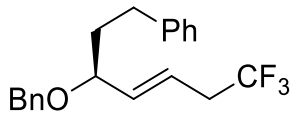
2.3ab **2.3ab**

General procedure followed and crude purified by column chromatography (eluent 20:1 hexane/EtOAc) to yield an inseparable mixture of products **2.3ab** and **2.3ab'** as a colourless oil (26.2 mg, 0.11 mmol, 79%, racemic, 10:1 positional isomers).

R_F 0.34 (20:1 hexane/EtOAc); ν_{max}/cm^{-1} 3028, 2972, 2859 (C-H), 1494, 1452 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 – 7.09 (10H + 10H', m, Ar-H, major + minor), 6.59 (1H, d, *J* = 16.0 Hz, =C$\underline{H}$Ph, major), 6.21 (1H, dd, *J* = 16.0, 7.7 Hz, =C$\underline{H}$CH, major), 5.89 – 5.49 (2H' m, =CH, minor), 4.83 (1H', d, *J* = 6.3 Hz, OCH, minor), 4.66 (1H, d, *J* = 11.9 Hz, PhOCHH), 4.48 (1H, d, *J* = 11.9 Hz, PhOCHH), 4.54 (2H', d, *J* = 0.9 Hz, OCH_2, minor), 4.16

(1H, p, *J* = 6.4 Hz, OCH, major), 1.76 (3H', d, *J* = 4.9 Hz, Me, minor), 1.43 (3H, d, *J* = 6.4 Hz, Me, major); ^{13}C NMR (75 MHz, $CDCl_3$) Major only δ 138.8 (C), 136.7 (C), 131.7 (CH), 131.4 (CH), 128.6 (CH), 128.4 (CH), 127.7 (CH), 127.4 (CH), 126.5 (CH), 75.9 (OCH), 70.1 (OCH_2), 21.8 (Me); CSP-HPLC (Chiralpak IB, hexane 1 mL min^{-1}) (*R*)-**2.3ab** 14.9 min and (*S*)-**2.3ab** 17.6 min.

(S,E)-(3-(Benzyloxy)-7,7,7-trifluorohept-4-en-1-yl)benzene (2.3pb)

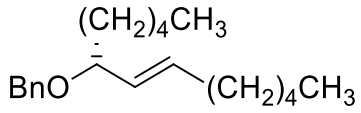


2.3pb

General procedure followed and crude purified by column chromatography (eluent 80:1 hexane/EtOAc) to yield impure product **2.3pb** as a colourless oil (42.2 mg, 0.12 mmol, 86%, ~80% purity by NMR, 95:5 e.r.).

R_F 0.47 (50:1 hexane/EtOAc); ν_{max}/cm^{-1} 3029, 2929, 2863 (C-H), 1496, 1454, 1429 (C-C Ar); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05-7.29 (5H, m, Ar-H), 5.61 (1H, dd, *J* = 15.6, 7.3 Hz, =C<u>H</u>CH), 5.52 (1H, dt, *J* = 15.6, 6.6 Hz, =C<u>H</u>CH_2), 4.50 (1H, d, *J* = 11.8 Hz, PhOC<u>H</u>H), 4.26 (1H, d, *J* = 11.8 Hz, PhOCH<u>H</u>), 3.70 (1H, td, *J* = 7.3, 5.5 Hz, HCO) 2.72 – 2.87 (2H, m, CH_2CF_3), 2.52 – 2.72 (2H, m, CH_2Ph), 1.86 – 1.99 (1H, m, OCHC<u>H</u>$_2$), 1.67 – 1.79 (1H, m, OCHC<u>H</u>$_2$) Assigned using COSY 2D NMR; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 141.8 (C), 138.4 (CH), 128.44 (CH), 128.41 (CH), 128.36 (CH), 128.3 (q, *J* = 212.8 Hz, CF_3), 127.8 (CH), 127.6 (CH), 125.8 (CH), 121.0 (q, *J* = 3.7 Hz, C<u>H</u>CH_2CF_3), 78.4 (CH), 70.3 (CH_2), 37.08 (q, *J* = 29.9 Hz, <u>C</u>H_2CF_3), 37.0 (CH_2), 31.5 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ -66.41 (t, *J* = 10.6 Hz); Found (FTMS p NSI+) $[M + NH_4]^+$ 352.1884, $C_{20}H_{25}F_3ON$ requires 352.1883; $[\alpha]_D^{22^\circ C}$ = -10.0 (c = 0.28 in $CHCl_3$); CSP-HPLC (Chiralpak IA, hexane, 0.5 ml min^{-1}) (*R*)-**2.3pb** 22.0 min and (*S*)-**2.3pb** 24.7 min.

(*R, E*)-((Tridec-7-en-6-yloxy)methyl)benzene (2.3qb)



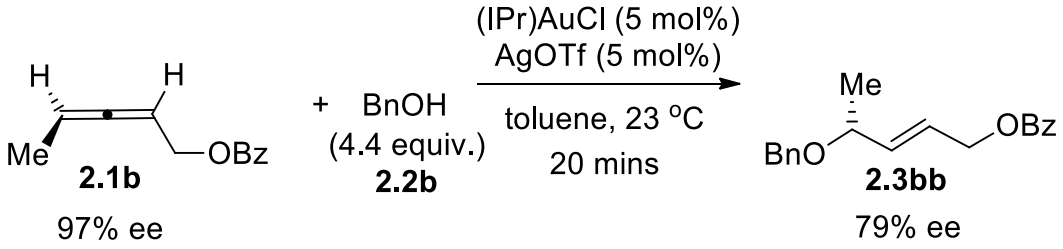
2.3qb

General procedure followed and crude purified by column chromatography (eluent 80:1 hexane/EtOAc) to yield product **2.3qb** as a colourless oil (33.2 mg, 0.11 mmol, 82%, 69:31 e.r.).

ν_{max}/cm^{-1} 2955, 2926, 2857 (C-H), 1454 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 – 7.23 (5H, m, Ar-H), 5.65 (1H, dt, *J* = 15.3, 6.7 Hz, =C<u>H</u>CH_2), 5.38 (1H, dd, *J* = 15.4, 8.3 Hz, =C<u>H</u>CH), 4.50 (1H, d, *J* = 12.0 Hz, OCHH), 4.25 (1H, d, *J* = 12.0 Hz, OCHH), 3.72 (1H, dt, *J* = 14.6, 6.5 Hz, OCH), 2.13 (2H, q, *J* = 6.8 Hz, =CHC<u>H_2</u>), 1.99 – 1.04 (14H, m, CH_2), 1.04 – 0.87 (6H, m, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2 (C), 134.3 (CH), 130.9 (CH), 128.3 (CH), 127.8 (CH), 127.3 (CH), 80.3 (CH), 69.6 (CH_2), 35.8 (CH_2), 32.2 (CH_2), 31.8 (CH_2), 31.4 (CH_2), 29.0 (CH_2), 25.2 (CH_2), 22.7 (CH_2), 22.5 (CH_2), 14.1 (CH_3), 14.1 (CH_3); Found (FTMS p NSI+) $[M + NH_4]^+$ 306.2791, $C_{20}H_{36}ON$ requires 306.2791; $[\alpha]_D$ = +14.1 (c = 1.28 in $CHCl_3$); CSP-HPLC (Chiralpak IA, hexane, 1 mL min^{-1}) (*R*)-**2.3qb** 5.2 min and (*S*)-**2.3qb** 5.6 min.

2.5.5 Determination of Absolute Configuration

Widenhoefer has previously shown, by comparison of **2.3bb** to known compounds, that under the conditions shown in Scheme 2.33, the *R*-enantiomer of **2.3bb** is formed.[68]



Scheme 2.33: Widenhoefer's conditions giving (*R*)-**2.3bb**

The conditions (Scheme 2.33) were repeated and the product obtained **2.3bb** produced the following HPLC trace (Figure 2.2).

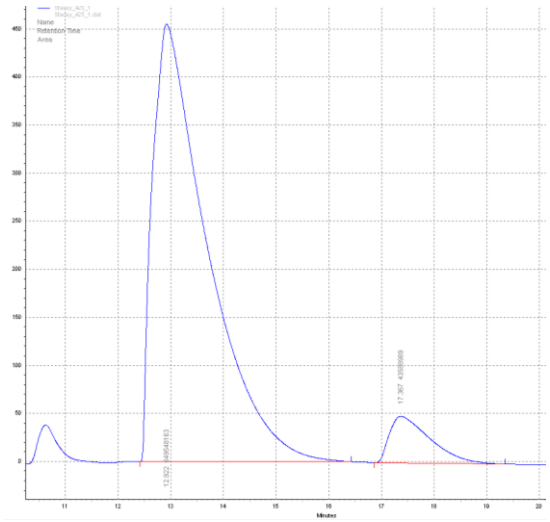


Figure 2.2: HPLC trace of product **2.3bb** obtained under Widenhoefer's conditions.[ϖ]

Under our conditions the following HPLC trace was obtained (Figure 2.3). This suggests our conditions are also producing the *R*-enantiomer.

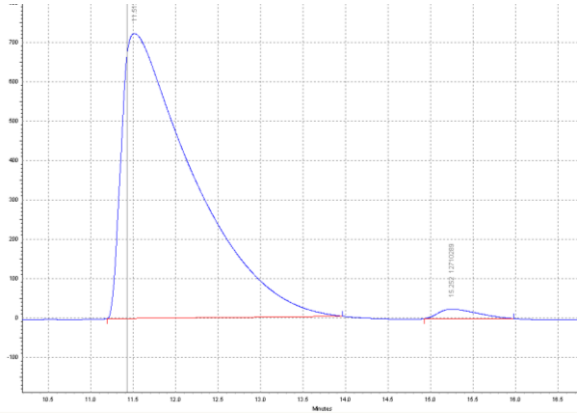
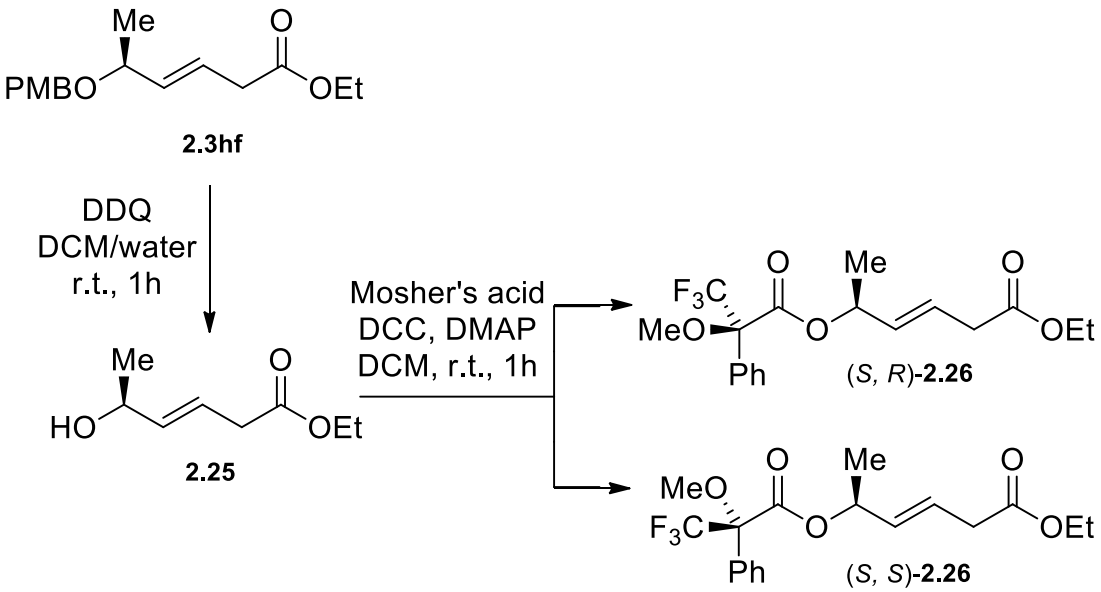


Figure 2.2: HPLC trace of product **2.3bb** under our conditions.[ϖ]

The absolute configuration of **2.3hf** was determined by Mosher's ester analysis using ^{1}H and ^{13}C NMR.[76]



Scheme 2.33: Synthetic route to Mosher's esters (*S, R*)-**2.26** and (*S, S*)-**2.26**

In the most represented configuration of a Mosher's ester the CF_3 group, the carbonyl and the H on the chiral carbon are all in the same plane. For Mosher's esters (*S, R*)-**2.26** and (*S, S*)-**2.26**, in their most represented configuration, the phenyl group will be in close proximity to either the alkene CH or methyl group. Since the phenyl group shields the nuclei of whichever group it is closest to, the NMR signal of that group is shifted upfield. This means that if alcohol **2.25** is the *S*-enantiomer (as expected) the Mosher's ester (S, *S*)-**2.26** will have a more upfield methyl group signal than the Mosher's ester (S, *R*)-**2.26** and the Mosher's ester (S, *R*)-**2.26** will have a more upfield alkene CH signal than the Mosher's ester (S, *S*)-**2.26**. This is indeed the case and can be represented as

$$\Delta\delta^{SR}_{\text{Me}} = \delta_{\text{Me}}(S) - \delta_{\text{Me}}(R)$$

$$\Delta\delta^{SR}_{\text{CHalkene}} = \delta_{\text{CHalkene}}(S) - \delta_{\text{CHalkene}}(R)$$

where if $\Delta\delta^{SR}_{\text{Me}} < 0$ and $\Delta\delta^{SR}_{\text{CHalkene}} > 0$ the alcohol is the *S*-enantiomer.

$$\Delta\delta^{SR}_{\text{Me}} = \delta_{\text{Me}}(S) - \delta_{\text{Me}}(R)$$

$$^{1}\text{H NMR } \Delta\delta^{SR}_{\text{Me}} = 1.39 - 1.46 = -0.17$$

$$^{13}\text{C NMR } \Delta\delta^{SR}_{\text{Me}} = 19.79 - 20.02 = -0.23$$

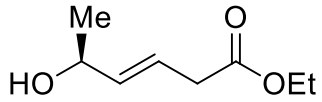
$$\Delta\delta^{SR}_{\text{CHalkene}} = \delta_{\text{CHalkene}}(S) - \delta_{\text{CHalkene}}(R)$$

^{1}H NMR $\Delta\delta^{SR}_{CHalkene}$ = 5.77* – 5.69* = + 0.08

*most downfield point of multiplet

^{13}C NMR could not be assigned without ambiguity

(*S,E*)-Ethyl 5-hydroxyhex-3-enoate (2.25)[77]

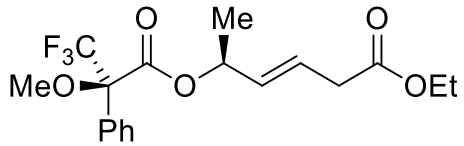


2.25

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (120 mg, 0.53 mmol, 1.2 equiv.) was added to a stirring solution of PMB ester **2.3hf** (123 mg, 0.44 mmol, 1 equiv.) in DCM (6 mL) and water (0.3 mL) and stirred for 1 h. A saturated solution of $NaHCO_3$ (20 mL) was added and the layers were separated. The aqueous layer was extracted with DCM, and the combined organic layers washed with brine, dried over $MgSO_4$ and concentrated. The mixture was purified by column chromatography (eluent: 2:1 hexane/EtOAc) to yield product **2.25** as a colourless oil (50.6 mg, 0.31 mmol, 71%).

R_F 0.23 (2:1 hexane/EtOAc); ν_{max}/cm^{-1} 3412 (OH), 2975 (C-H), 1733 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 – 5.73 (1H, m, =C<u>H</u>CH$_2$), 5.73 – 5.62 (1H, m, =C<u>H</u>CH), 4.34 (1H, p, *J* = 6.2 Hz, OCH), 4.17 (2H, qd, *J* = 7.1, 0.9 Hz, OC<u>H</u>$_2$), 3.08 (2H, d, *J* = 6.6 Hz, CHC<u>H</u>$_2$), 1.75 (1H, br d, *J* = 14.7 Hz, OH), 1.35 – 1.23 (6H, m, CH$_2$C<u>H</u>$_3$ + CHC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7 (C), 138.1 (CH), 122.1 (CH), 68.4 (CH), 60.7 (CH_2), 37.6 (CH_2), 23.1 (CH_3), 14.2 (CH_3).

(*S,E*)-Ethyl 5-(((R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)hex-3-enoate ((*S, R*)-2.26)[78]



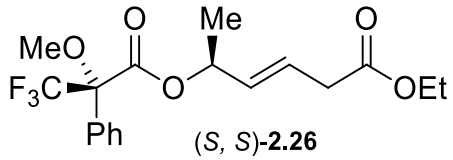
(*S, R*)-**2.26**

To a stirring solution of alcohol **2.25** (19.0 mg, 0.12 mmol, 1.0 equiv.) in DCM (3.0 mL) (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (84.2 mg, 0.36 mmol, 3.0 equiv.), dicyclohexylcarbodiimide (74.4 mg, 0.36 mmol, 3.0 equiv.), and 4-dimethylaminopyridine (44.0 mg, 0.36 mmol, 3.0 equiv.) were added sequentially. The

reaction mixture was stirred for 1 hour at room temperature, passed through a silica plug (DCM) dried over $MgSO_4$ and concentrated. The mixture was purified by column chromatography (eluent: 14:1 then 10:1 hexane/Et_2O) to yield product (*S, R*)-**2.26** as a colourless oil (34.2 g, 0.09 mmol, 73%).

R_F 0.36 (9:1 hexane/EtOAc); ν_{max}/cm^{-1} 2984 (C-H), 1737 (C=O), 1164 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 – 7.48 (2H, m, Ar-H), 7.48 – 7.36 (3H, m, Ar-H), 5.89 (1H , dt, *J* = 14.6, 7.0 Hz, =C<u>H</u>CH_2), 5.69 – 5.51 (2H, m, =C<u>H</u>CH), 4.17 (2H, q, *J* = 7.1 Hz, OC<u>H_2</u>CH_3), 3.59 (3H, s, OCH_3), 3.07 (2H, d, *J* = 6.9 Hz, OCH), 1.46 (3H, d, *J* = 6.3 Hz, CHC<u>H_3</u>), 1.28 (3H, t, *J* = 7.1 Hz, CH_2C<u>H_3</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0 (C), 165.6 (C), 132.4 (C), 131.9 (CH), 129.5 (CH), 128.3 (CH), 127.3 (CH), 126.1 (CH), 123.3 (q, CF_3), 73.1 (CH), 60.8 (CH_2), 55.4 (CH_3), 37.6 (CH_2), 20.0 (CH_3), 14.1 (CH_3).

(*S,E*)-Ethyl 5-(((S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)hex-3-enoate ((S, R)-**2.26)**[78]

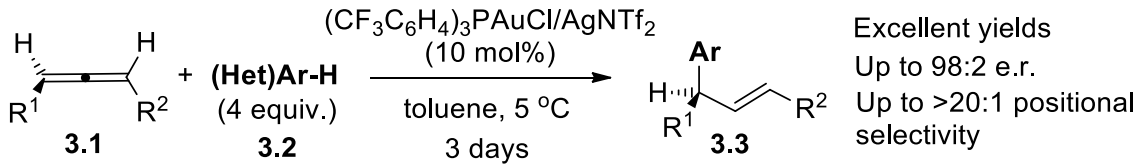


(*S, S*)-**2.26**

Prepared as above using (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid.

R_F 0.36 (9:1 hexane/EtOAc); ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 – 7.49 (2H, m, Ar-H), 7.49 – 7.35 (3H, m, Ar-H), 5.96 (1H , dt, *J* = 14.6, 7.0 Hz, =C<u>H</u>CH_2), 5.77 – 5.58 (2H, m, =C<u>H</u>CH), 4.17 (2H, q, *J* = 7.1 Hz, OC<u>H_2</u>CH_3), 3.59 (3H, s, OCH_3), 3.10 (2H, d, *J* = 6.9 Hz, OCH), 1.39 (3H, d, *J* = 6.3 Hz, CHC<u>H_3</u>), 1.28 (3H, t, *J* = 7.1 Hz, CH_2C<u>H_3</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0 (C), 165.7 (C), 132.4 (C), 132.0 (CH), 129.5 (CH), 128.4 (CH), 127.3 (CH), 126.3 (CH), 123.3 (q, CF_3), 73.2 (CH), 60.8 (CH_2), 55.4 (CH_3), 37.6 (CH_2), 19.8 (CH_3), 14.1 (CH_3).

Chapter 3: Chirality transfer in the gold-catalysed hydroarylation of allenes



Acknowledgments

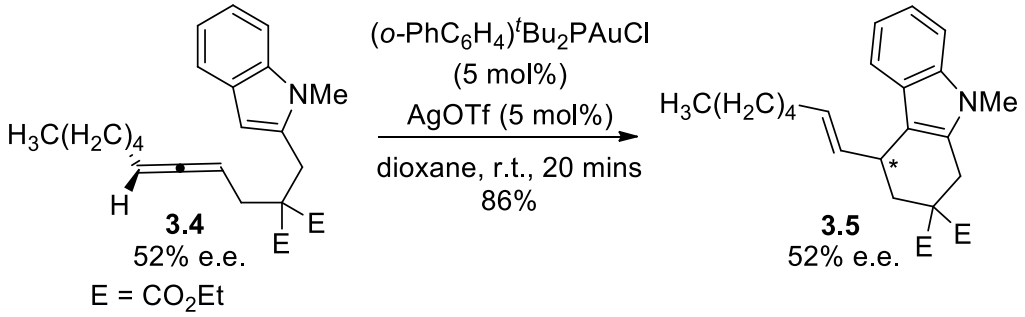
The author would like to thank Luke Kinsman (MChem project student 2016-2017) for his early optimisation work on this project and Stuart Angiolini (undergraduate summer student 2017) for his assistance with the nucleophile scope. All work completed by Stuart is clearly marked with ‡.

3.1 Introduction

3.1.1 Previous work in the hydroarylation of allenes

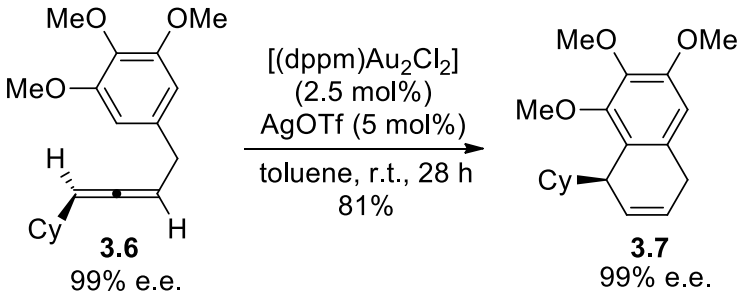
After the successful development of conditions which provide excellent chirality transfer in the hydroalkoxylation of allenes,[72] we looked to expand our methodology to other nucleophiles. After searching the literature we found that although there had been several reports of successful hydroarylation protocols (see below), general conditions allowing the reaction of both indoles and electron-rich arenes had not been reported. Most importantly, efficient chirality transfer in the intermolecular hydroarylation of allenes had not yet been achieved.

The hydroarylation of allenes was first reported as an intramolecular reaction with tethered indoles. Encouragingly, Widenhoefer and co-workers were able to demonstrate, that under their conditions, excellent chirality transfer can be achieved (Scheme 3.1).[30]



Scheme 3.1: First reported intramolecular hydroarylation with chirality transfer[30]

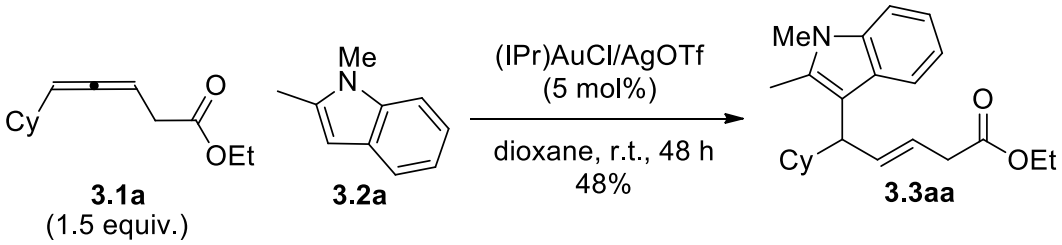
Later, tethered electron-rich arenes, thiophenes and benzothiophenes were also reported in the intramolecular hydroarylations of allenes, again with excellent chirality transfer (Scheme 3.2).[33]



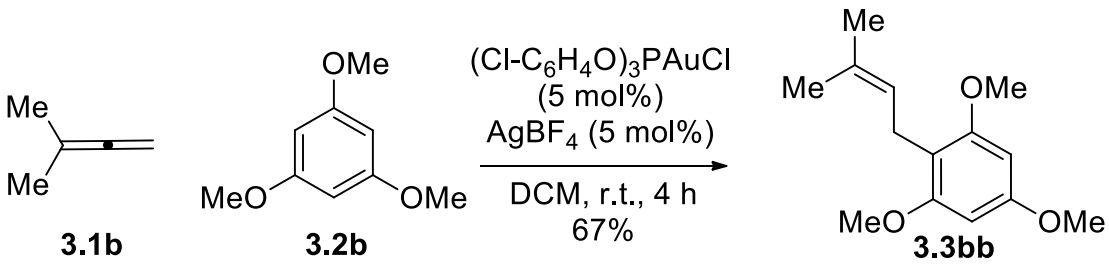
Scheme 3.2: Example of chirality transfer in hydroarylation with electron-rich arene[33]

The publications mentioned above, report examples with excellent chirality transfer using 1,3-disubstituted allenes, which is the same substitution pattern as the intermolecular substrates previously studied (Chapter 2).[72] However, as previously discussed, the intermolecular version of hydrofunctionalisations is more challenging as the selectivity derived from the intramolecular nature of these reactions is lost. Perhaps for this reason, the intermolecular hydroarylation of allenes with chirality transfer has been far less extensively investigated. The racemic intermolecular hydroarylation of allenes has been studied, however.

In 2009, Widenhoefer reported the gold-catalysed hydroarylation of a range of allenes using indoles as nucleophiles. Although this work included 1,3-disubtituted allenes, no attempt at chirality transfer was reported (Scheme 3.3).[38]



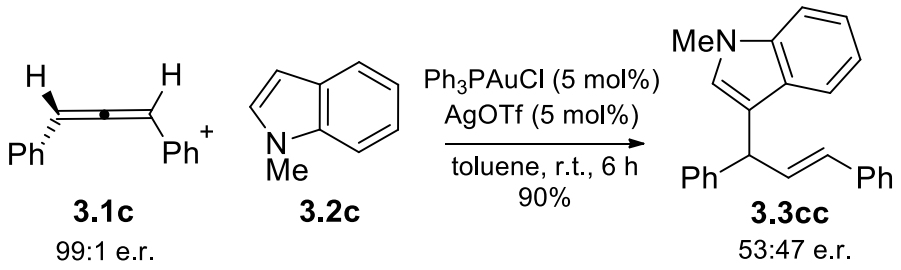
Scheme 3.3: Gold(I)-catalysed hydroarylation of a 1,3-disubstituted allene[38]



Scheme 3.4: Intermolecular hydroarylation of allenes with electron-rich arenes[79]

Other nucleophiles have also been used in gold-catalysed hydroarylations with some success (Scheme 3.4). In Gagné and co-workers' 2009 report,[79] as well as in the only other similar report found,[39] the conditions are specific to only a fairly narrow scope of arenes and no other heterocycles. The allene scope reported in both of these publications are also limited to only 1-substituted or 1,1-disubstituted allenes. The gold-catalysed hydroarylation of 1,3-disubsituted allenes with arenes had not been achieved prior to the project described in this chapter.

More recently, Che and co-workers disclosed their work on hydroarylation of allenes with indoles, including their initial attempts at achieving chirality transfer with 1,3-diphenyl-substituted allene **3.1c**.[52] They reported totally racemic products (Scheme 3.5), citing gold-catalysed allene substrate racemisation as the reason for the lack of chirality transfer observed.



3.1c 99:1 e.r. **3.2c** **3.3cc** 53:47 e.r.

Scheme 3.5: Hydroarylation of enantioenriched allene – Che's initial conditions[52]

Che and co-workers were able to utilise the gold-catalysed allene substrate racemisation to develop the first chiral, digold-catalysed, enantioselective hydroarylation reaction via dynamic kinetic resolution (see Section 1.3.5). However, the best example of enantiomeric excess achieved was only 63%.[52]

It was clear from reading the literature that it would be an important advancement in the field if conditions could be developed which allowed for chirality transfer in the hydroarylation of 1,3-disubstituted allenes. Additionally, it would be particularly advantageous if these hydroarylations conditions could also be applied to other heterocycles and electron-rich arenes. Following the successful development of

conditions which provide excellent chirality transfer in the related hydroalkoxylation of allenes (Chapter 2), we felt confident that the aims above could be achieved.

3.1.2 Relevant conclusions from previous work (Chapter 2)

During the project outlined in Chapter 2 it was shown that the main reason for loss of chirality transfer was the gold-catalysed racemisation of the allene starting material and that this could be avoided by tuning the conditions to reduce the reactivity of the catalyst. It was shown that the temperature, equivalents of nucleophile and solvent all contribute to slowing down the catalysts reactivity and helping to prevent allene racemisation.

Another important conclusion drawn from the hydroalkoxylation project (Chapter 2) was the types of allenes which are best suited to gold-catalysed hydrofunctionalisation with chirality transfer; chiefly allenes with inductively withdrawing groups on one substituent. Inclusion of an inductively withdrawing group in the allene allows for selective attack at one end of the allene. It is thought that the functionality draws electron density away from the carbon-carbon bond of the allene closest to it (π^2, Figure 3.1) and thereby promotes reaction at the more remote and electron-rich carbon-carbon bond (π^1, Figure 3.1).

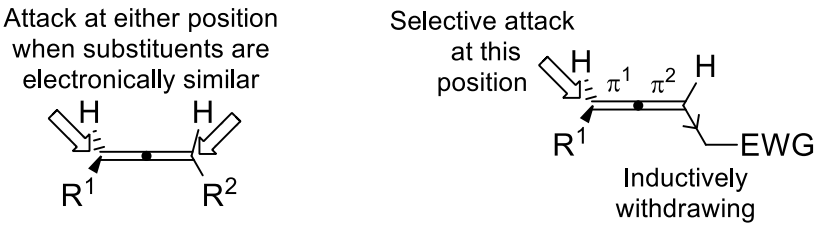
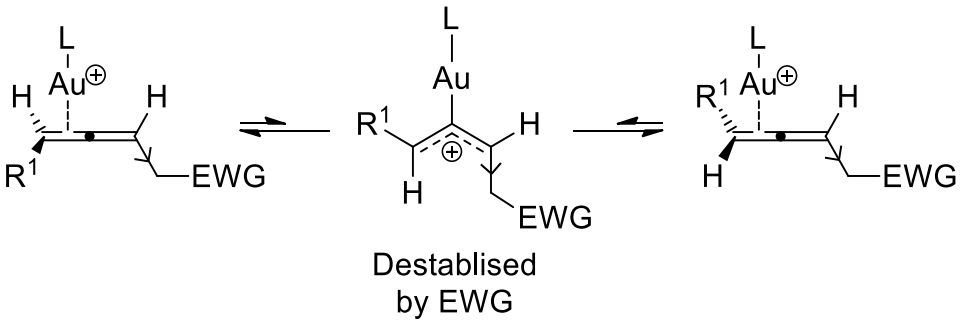


Figure 3.1: Positional selectivity through inductively withdrawing group

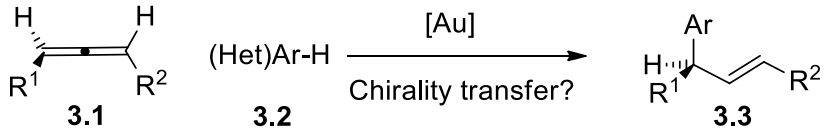
As well as providing good positional selectivity, having an inductively withdrawing group on the allene is believed to destabilise the transition state of the allene racemisation mechanism (Scheme 3.6). This is thought to slow down the racemisation, thereby allowing better chirality transfer for allenes with more inductively withdrawing substituents.



Scheme 3.6: Gold-catalysed 1,3-disubstituted allene racemisation

3.2 Project aims

The aim of this project is to achieve the first efficient chirality transfer in the hydroarylation of 1,3-disubstituted allenes (Scheme 3.7).



Scheme 3.7: Is efficient chirality transfer in the hydroarylation of 1,3-disustituted allenes possible?

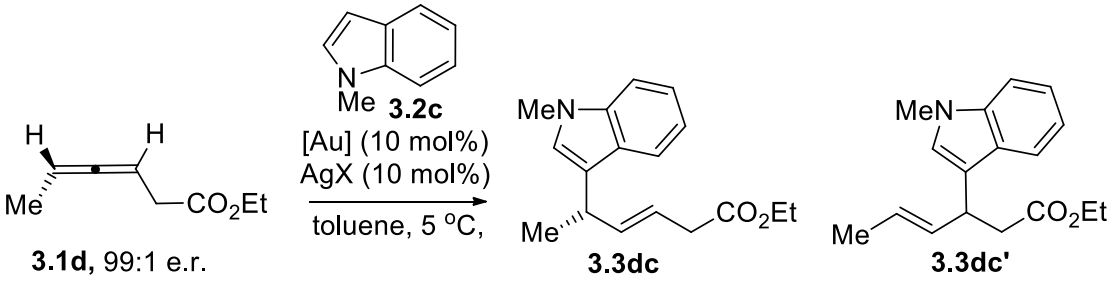
As with the hydroalkoxylation of allenes (Chapter 2), the main challenge is the competing gold-catalysed racemisation of the allene starting material **3.1**. We planned to approach this challenge by adapting the reaction conditions to allow the gold-catalysed hydroarylation to occur without the unwanted gold-catalysed allene racemisation.

Upon developing conditions for good chirality transfer, we hoped to investigate a range of 1,3-disubstituted allenes with inductively withdrawing groups on one substituent. We also aimed to expand the nucleophile scope as much as possible. Firstly, we planned to investigate indoles which have been most heavily studied in previous, racemic work[52, 80] and secondly, electron-rich arenes and other heterocycles since no reports of hydroarylation of these nucleophiles with 1,3-disubstituted allenes were known. To accomplish the hydroarylation of 1,3-disubstituted allenes with a range of aryls and achieve efficient chirality transfer would be a significant improvement to the field of allene hydroarylations.

3.3 Results and Discussion

3.3.1 Optimisation of hydroarylation reaction

The optimisation of hydroarylation conditions which would allow for chirality transfer was carried out with the ester-functionalised allene **3.1d** and *N*-methylindole **3.2c** as model substrates. The conditions initially used were based on Che's conditions (Scheme 3.5)[52] with a lower temperature (10 °C), longer reaction time (1 day) and using more convenient silver-free Gagosz catalyst[81] (PPh_3AuNTf_2). These conditions (Entry 1, Table 3.1) gave an encouraging 27% yield and good positional selectivity (10:1 **3dc**:**3dc'**).



Entry	Conc (mol/L)	Equiv. **3.2c**	Time (days)	Catalyst	**3.3dc**: **3.3dc'**[a]	**3.3dc** e.r.[b]	NMR conv. (%)[a]	Yield (%)[c]
1[d]	0.15	4	1	PPh_3AuNTf_2	10:1	N.D.	N.D.	27
2[d]	0.40	4	1	PPh_3AuNTf_2	8:1	N.D.	N.D.	39
3[d]	0.75	4	1	PPh_3AuNTf_2	7:1	87:13	N.D.	50
4	1.50	4	1	PPh_3AuNTf_2	7:1	90:10	N.D.	41
5	1.50	2	1	PPh_3AuNTf_2	7:1	91:9	N.D.	37
6	1.50	4	1	PPh_3AuCl/ $AgBF_4$	N.D.	N.D.	19	N.D.
7	1.50	4	1	PPh_3AuCl/ $AgClO_4$	N.D.	N.D.	19	N.D.
8	1.50	4	1	(IMes)AuCl/ $AgNTf_2$	5:1	77:23	N.D.	55
9	1.50	4	1	$(CF_3C_6H_4)_3PAuCl$/ $AgNTf_2$	11:1	93:7	N.D.	60
10	1.50	4	3	$(CF_3C_6H_4)_3PAuCl$/	11:1	93:7	N.D.	67

				$AgNTf_2$				
11	1.50	2	3	$(CF_3C_6H_4)_3PAuCl$/ $AgNTf_2$	10:1	94:6	N.D.	59
12	0.40	4	3	$(CF_3C_6H_4)_3PAuCl$/ $AgNTf_2$	12:1	90:10	N.D.	55

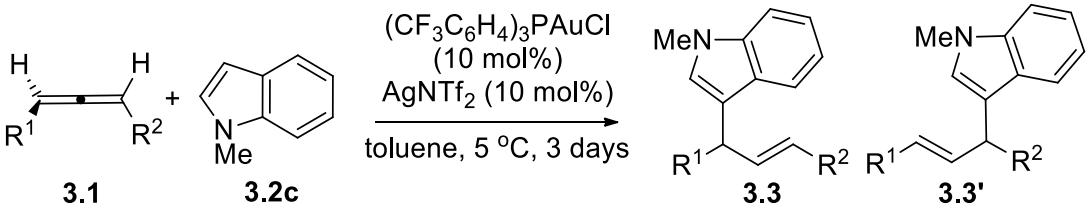
[a] Determined by ^{1}H NMR analysis. >20:1 E:Z by ^{1}H NMR analysis. [b] Determined by CSP-HPLC. [c] Isolated yields. [d] Carried out at 10 ^{o}C. N.D. = not determined.

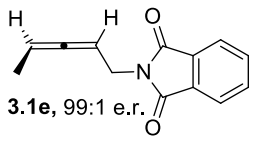
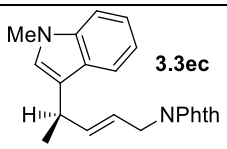
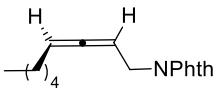
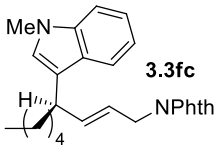
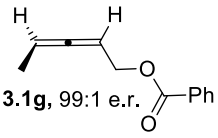
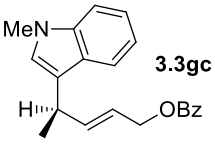
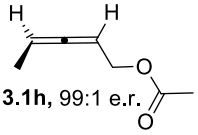
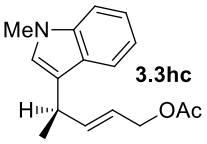
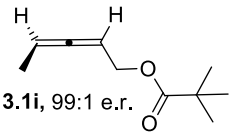
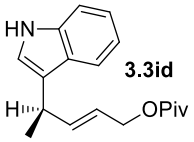
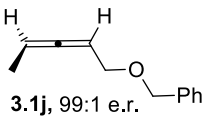
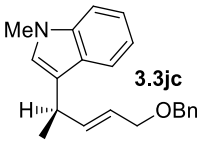
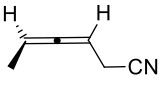
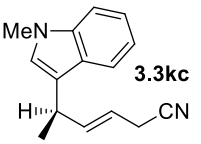
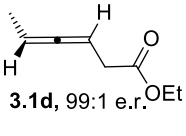
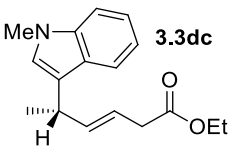
Table 3.1: Optimisation of the hydroarylation of allene **3.1d** with indole **3.2c**

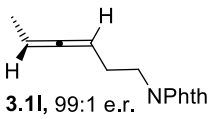
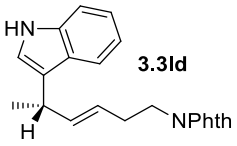
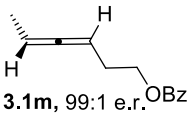
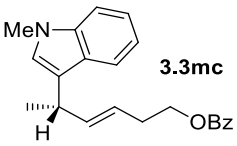
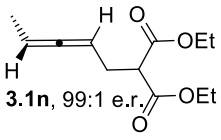
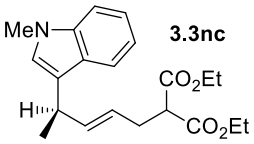
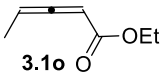
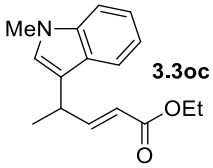
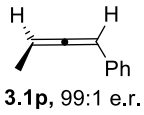
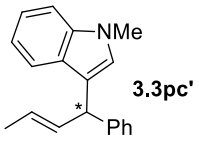
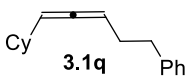
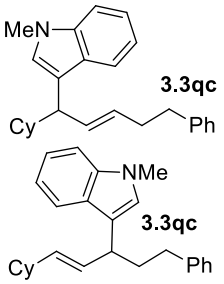
After this initial result we looked to increase the yield of the reaction by increasing the concentration (Entries 1-3, Table 3.1). Pleasingly, the yield was improved to 50% and the product **3dc** was obtained in 87:13 e.r. (Entry 3, Table 3.1). The reaction temperature was then reduced to 5 ^{o}C along with an increase in concentration, providing product **3dc** in better slightly better e.r. (7:1 **3dc**:**3dc'**, 90:10 e.r., 41%, Entry 4, Table 3.1). Reducing the equivalents of indole was found to be slightly detrimental to the yield (37%, Entry 5, Table 3.1) and alternative counterions were found to be unfavorable, giving only 19% conversion by ^{1}H NMR analysis (Entries 6 and 7, Table 3.1). However, varying the ligand on the catalyst had a much more pronounced effect. Using the NHC ligand IMes in place of PPh_3 improved the yield of the reaction but decreased the selectivity substantially (5:1 **3dc**:**3dc'**, 77:23 e.r., 55%, Entry 8, Table 3.1). To our delight, the more active catalyst $(CF_3C_6H_4)_3PAuCl$ greatly improved the chirality transfer as well as the positional selectivity and yield of the reaction (11:1 **3dc**:**3dc'**, 93:7 e.r., 60%, Entry 9, Table 3.1). Lengthening the reaction time to 3 days improved the yield to 67% and gave our optimised conditions for the reaction (Entry 10, Table 3.1). Finally, it was confirmed that lowering the equivalents of nucleophile **3.2c** or reducing the concentration was detrimental to the yield of the reaction (58% and 55% respectively, Entries 11 and 12, Table 3.1).

With our optimised conditions in hand, a range of allenes were prepared in the same manner as described in Section 2.3.2 and subjected to the newly optimised gold-catalysed hydroarylation reaction. Upon commencing the substrate scope we were delighted to find that many of the allenes chosen outperformed the original ester containing allene **3.1d** used in the optimisation study (Section 3.3.2).

3.3.2 Allene scope



Entry	Allene	Major product	Yield[a]	**3.3**:**3.3'**[b]	e.r. [c]
1	 **3.1e,** 99:1 e.r.	 **3.3ec**	94%	>20:1	97:3
2	 **3.1f**, 98:2 e.r.	 **3.3fc**	81%	>20:1	98:2
3	 **3.1g,** 99:1 e.r.	 **3.3gc**	95%	15:1	97:3
4	 **3.1h,** 99:1 e.r.	 **3.3hc**	74%	15:1	97:3
5[d]	 **3.1i,** 99:1 e.r.	 **3.3id**	58%	8:1	94:6
6	 **3.1j,** 99:1 e.r.	 **3.3jc**	74%	6:1	85:15
7	 **3.1k,** 98:2 e.r.	 **3.3kc**	77%	>20:1	98:2
8	 **3.1d,** 99:1 e.r.	 **3.3dc**	67%	11:1	93:7

9[d]	 **3.1l**, 99:1 e.r.	 **3.3ld**	97%	11:1	76:24
10	 **3.1m**, 99:1 e.r.	 **3.3mc**	82%	7:1	92:8
11	 **3.1n**, 99:1 e.r.	 **3.3nc**	96%	18:1	87:13
12[e]	 **3.1o**	 **3.3oc**	23%	>20:1	N.D.
13	 **3.1p**, 99:1 e.r.	 **3.3pc'**	82%	1:3	**3.3pc'** 79:21 **3.3pc** 53:47
14	 **3.1q**	 **3.3qc** **3.3qc**	28%	1.4:1	N.D.

[a] Yield of isolated products; all >20:1 E:Z. [b] Determined by ^{1}H NMR analysis. [c] Determined by CSP-HPLC. [d] Indole **3.2d** was used as the product from the reaction of indole **3.2c** could not be separated by CSP-HPLC. [e] Reaction carried out at r.t. (only trace product observed at 5 ^{o}C). N.D. = not determined.

Table 3.2: Allene scope of hydroarylation reaction

To our delight, one of the first allenes subjected to the optimised conditions **3.1e** proceeded with perfect positional selectivity as well as excellent yield and chirality transfer (**3.3ec**, 94%, >20:1, 97:3 e.r., Entry 1, Table 3.2). Pleasingly, replacing the Me group in **3.1e** with a longer alkyl chain (**3.1f**) was not detrimental to the reaction, and the product was formed in good yield with high selectivity (**3.3fc**, 81%, >20:1, 98:2 e.r.,

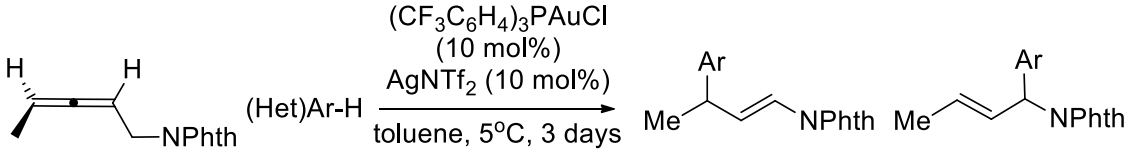
Entry 2, Table 3.2). Excellent chirality transfer and yield was also obtained for the OBz-substituted allene **3.1g** albeit with slightly lower positional selectivity (**3.3gc**, 95%, 15:1, 97:3 e.r., Entry 3, Table 3.2). As with the hydroalkoxylation project (Chapter 2) a range of other protected allenols were investigated (Entries 4–6, Table 3.2). Acetyl protected allenol **3.1h** reacted smoothly to provide the desired product with high e.r. and with good positional selectivity (**3.3hc**, 74%, 15:1, 97:3 e.r., Entry 4, Table 3.2). However, some positional selectivity was lost with the pivaloyl-protected allenol **3.1i**; Gratifyingly though, the e.r. of the product was still high (**3.3id**, 58%, 8:1, 96:4 e.r., Entry 5, Table 3.2). Removal of the carbonyl group (**3.1j**) gave a similar drop in positional selectivity but along with a decrease in chirality transfer (**3.3jc**, 74%, 6:1, 85:15 e.r., Entry 6, Table 3.2). This is thought to be due to the lower inductive withdrawing ability of the OBn group (Entry 6 *vs.* Entries 3-5; see Section 3.1.2). Much more pleasingly, cyano-substituted allene **3.1k** performed very well under our conditions giving perfect chirality transfer (allene **3.1k**, 98:2 e.r.) and positional selectivity (**3.3kc**, 77%, >20:1, 98:2 e.r., Entry 7, Table 3.2).

In keeping with the thinking that the inductively withdrawing group helps to prevent gold-catalysed allene racemisation and thereby facilitate chirality transfer (Section 3.1.2), moving the functionality farther from the allene moiety reduced the e.r. of the products obtained (Entry 9 *vs.* Entry 1 and Entry 10 *vs.* Entry 3). Positional selectivity was also lost by moving the inductively withdrawing group farther from the allene (see Section 3.1.2). Pleasingly, the products from this investigation were still prepared in good yield and reasonably high selectivity (**3.3ld**, 97%, 11:1, 76:24 e.r., Entry 9 and **3.3mc**, 82%, 7:1, 98:2 e.r., Entry 10, Table 3.2). Again looking at substrates with functionality far removed from the allene moiety, allene **3.1n** was investigated next. To our delight, despite the distant position of the inductively withdrawing group, the reaction proceeded well with excellent yield as well as good positional selectivity and chirality transfer (**3.3nc**, 96%, 18:1, 87:13 e.r., Entry 11, Table 3.2). Interestingly, when the ester moiety is in direct conjugation with the allene, the reaction becomes very sluggish. Substrate **3.3o** gave only traces of product at 5 ^{o}C and a poor yield at room temperature (**3.3oc**, 23%, >20:1, Entry 12, Table 3.2). This is thought to be because the allene is comparatively electron-poor.

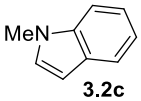
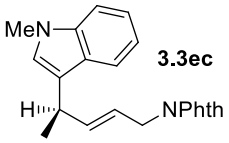
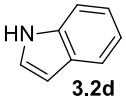
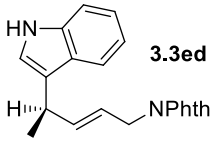
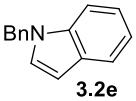
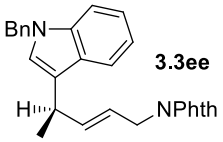
The phenyl-substituted allene **3.1p**, which was also used as a substrate during the hydroalkoxylation project (Chapter 2), was investigated next. Under the hydroalkoxylation conditions this allene gave totally racemic product and showed preferential reaction at the position farthest from the phenyl group. The racemic product obtained in the hydroalkoxylation reaction was thought to be caused by the quick racemisation of the allene due to stabilisation of the transition state of the allene racemisation (see Section 2.3.5). Surprisingly, under hydroarylation conditions the allene was not fully racemised, proceeding with moderate chirality transfer and giving the unexpected positional isomer as the major product (**3.3pc'**, 82%, 1:3, 79:21 e.r., Entry 13, Table 3.2). Interestingly, previous racemic studies of hydroarylation with this substrate resulted in no positional selectivity (1:1.2).[38]

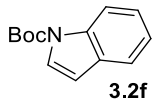
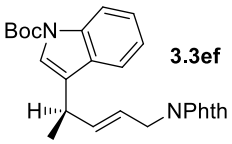
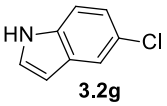
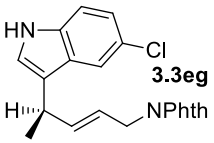
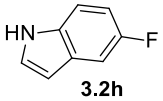
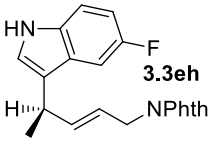
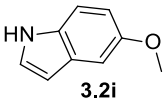
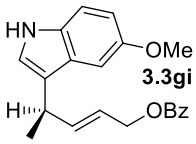
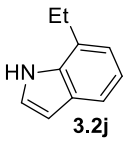
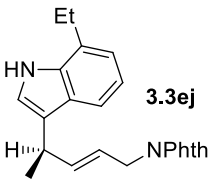
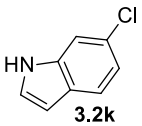
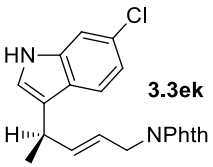
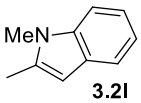
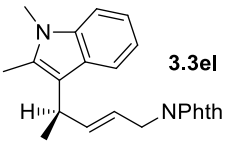
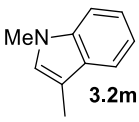
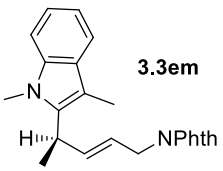
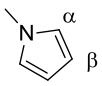
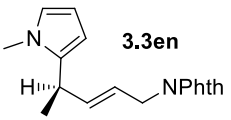
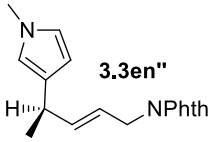
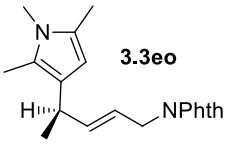
Finally, allene **3.1q** was subjected to the hydroarylation conditions (**3.3qc**, 28%, 1.4:1, Entry 14, Table 3.2). As expected, since the substituents are electronically similar, the positional selectivity is very poor for this substrate, confirming that positional selectivity is determined by electronic and not steric factors.

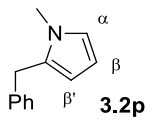
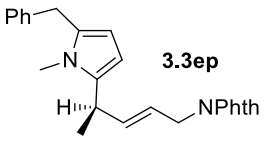
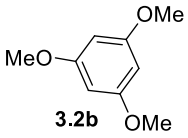
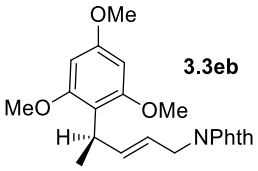
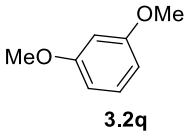
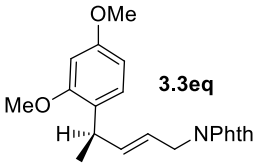
3.3.3 Nucleophile scope



3.1e, 99:1 e.r. **3.2** **3.3** **3.3'**

Entry	(Het)Ar-H	Major product	Yield[a]	**3.3**:**3.3'**[b]	e.r.[c]
1	 **3.2c**	 **3.3ec**	94%	>20:1	97:3
2	 **3.2d**	 **3.3ed**	89%	>20:1	95:5
3	 **3.2e**	 **3.3ee**	99%	>20:1	95:5

4	 **3.2f**	 **3.3ef**	32%	18:1	55:45
5	 **3.2g**	 **3.3eg**	96%	15:1	85:15
6‡	 **3.2h**	 **3.3eh**	90%	>20:1	89:11
7[d]	 **3.2i**	 **3.3gi**	67%	11:1	97:3
8‡	 **3.2j**	 **3.3ej**	84%	>20:1	96:4
9	 **3.2k**	 **3.3ek**	98%	15:1	82:18
10	 **3.2l**	 **3.3el**	92%	>20:1	98:2
11	 **3.2m**	 **3.3em**	48%	>20:1	82:18
12	 **3.2n**	 **3.3en**  **3.3en''**	58% 1:1 α/β[e]	>20:1	N.D.
13	 **3.2o**	 **3.3eo**	41% 48%[f]	>20:1	98:2

14	 **3.2p**	 **3.3ep**	40% major[g] 5:1:1 α/β/β'[d]	5:1	N.D.
15	 **3.2b**	 **3.3eb**	98%	>20:1	90:10
16	 **3.2q**	 **3.3eq**	97%	10:1	57:43

[a] Combined yield of isolated products; all >20:1 E:Z. [b] Determined by ^{1}H NMR analysis. [c] Determined by CSP-HPLC. [d] Allene **3.1g** was used as the product from the reaction of allene **3.2e** could not be separated by CSP-HPLC. [e] Ratio of isomers obtained by reaction at different positions of the pyrrole. Determined by ^{1}H NMR analysis. [f] 15 mol% catalyst. [g] Yield of the major isomer. N.D. = not determined.

Table 3.3: Nucleophile scope of hydroarylation reaction

The nucleophile scope of the reaction was investigated starting with a range of indoles. The *N*-substitution of the indole was varied first with *N*-methylindole **3.2c**, unsubstituted indole **3.2d** and *N*-benzylindole **3.2e** all reacting very smoothly (**2.3ec**-**2.3ee**, >89%, >20:1, >95:5 e.r., Entries 1-3, Table 3.3). The Boc protected indole **3.2f** however, reacted sluggishly, giving a poor yield and almost no chirality transfer (**3.3ef**, 32%, 18:1, 55:45 e.r., Entry 4, Table 3.3). This is likely due to the electron withdrawing nature of the Boc group making the indole less nucleophilic and thus slowing down the rate of the hydroarylation reaction. It is thought that since the hydroarylation reaction is slower, the competing allene racemisation can occur, resulting in poor chirality transfer to the product **3.3ef**.

5-Substituted indoles were investigated next (Entries 5-7, Table 3.3), with Cl- and F-substituted indoles (**3.2g** and **3.2h**) performing well in the reaction albeit with a slight reduction in chirality transfer (**3.3eg**, 96%, 15:1, 85:15 e.r., Entry 5 and **3.3eh**, 90%, >20:1, 89:11 e.r., Entry 6, Table 3.3). Interestingly, the more electron-rich MeO-substituted indole **3.2i**[82] performed better in terms of chirality transfer (**3.3gi**, 67%,

11:1, 97:3 e.r., Entry 7, Table 3.3). As before, the increased efficiency of chirality transfer seen in Entry 7 compared to Entries 5 and 6 is thought to be due to the less electron-rich nucleophiles (**3.2g** and **3.2h**) undergoing the hydroarylation reaction more slowly and so allowing for competing allene racemisation to occur.

7-Ethyl (**3.2j**) and 6-Cl (**3.2k**) reacted smoothly in the reaction, with the more electron-rich Et-substituted indole **3.2j** outperforming Cl-substituted indole **3.2k** with regard to chirality transfer (**3.3ej**, 84%, >20:1, 96:4 e.r., Entry 8 *vs.* **3.3ek**, 98%, 15:1, 82:18 e.r., Entry 9, Table 3.3). Pleasingly, 1,2-methyl indole **3.2l** provided an excellent yield, perfect positional selectivity and excellent chirality transfer (**3.3el**, 92%, >20:1, 98:2 e.r., Entry 10, Table 3.3). Perhaps predictably, when the most reactive 3-position of the indole is blocked, a drop in yield is observed and the e.r. of the product is lower (**3.3em**, 48%, >20:1, 82:18 e.r., Entry 11, Table 3.3). This is presumably again due to slower reacting nucleophiles allowing competing allene racemisation to occur.

Looking to expand the scope of the reaction beyond indoles, we investigated using pyrroles as nucleophiles (Entries 12-14, Table 3.3). Gagné previously found *N*-methylpyrrole **3.2n** to be unreactive under his gold-catalysed hydroarylation conditions.[79] However, under our conditions the reaction provided a reasonable yield and proceeded with good positional selectivity on the allene (**3.3en**, 58%, >20:1, Entry 12, Table 3.3). However, to our surprise, no regioselectivity was observed between reaction at the α and β position of the pyrrole (**3.3en**:**3.3en"** 1:1, Entry 12, Table 3.3). In order to overcome this unexpected complication, 1,3,5-trimethylpyrrole **3.3o** was subjected to the hydroarylation reaction and to our delight reacted very smoothly (**3.3eo**, 41%, >20:1, 98:2 e.r., Entry 13, Table 3.3). The yield could not be improved by increasing the reaction time or equivalents of pyrrole but was raised slightly to 48% by changing the catalyst loading to 15 mol%. Intrigued by the results obtained for **3.2n** (Entry 12, Table 3.3) and the success of **3.3o** (Entry 13, Table 3.3) a monosubstituted *N*-methylpyrrole **3.2p** was investigated next. Gratifyingly, the reaction did occur preferentially at the α-position of the pyrrole albeit with only moderate selectivity over the other two positions (5:1:1, Entry 14, Table 3.3).

The final two nucleophiles investigated were electron-rich arenes (Entries 15-16, Table 3.3) which had not previously been reported in intermolecular gold-catalysed hydroarylation of 1,3-disubstituted allenes. Pleasingly however, 1,3,5-trimethoxybenzene **3.3b** reacted smoothly to give **3.3eb** in excellent yield, positional selectivity and good chirality transfer (**3.3eb**, 98%, >20:1, 90:10 e.r., Entry 15, Table 3.3). Unfortunately, although the yield obtained is excellent, removing one methoxy group renders the arene (**3.3q**) not nucleophilic enough for efficient chirality transfer to occur (**3.3eq**, 97%, 10:1, 57:43 e.r., Entry 16, Table 3.3). Disappointingly, other less nucleophilic (hetero)aryls such as benzofurans, 2-methylfuran, 2-methoxythiophene, methoxybenzene and pentamethylbenzene failed to react under our hydroarylation conditions.

The absolute configuration of product **3.3eb** was determined by x-ray diffraction analysis and the absolute configuration of all other products was inferred by analogy. Although there are two independent molecules in the asymmetric unit of the crystal and one of those molecules is disordered, it can be calculated that there is 78% *R* and 22% *S* in the crystal and so the absolute stereochemistry can be assigned as *R.*

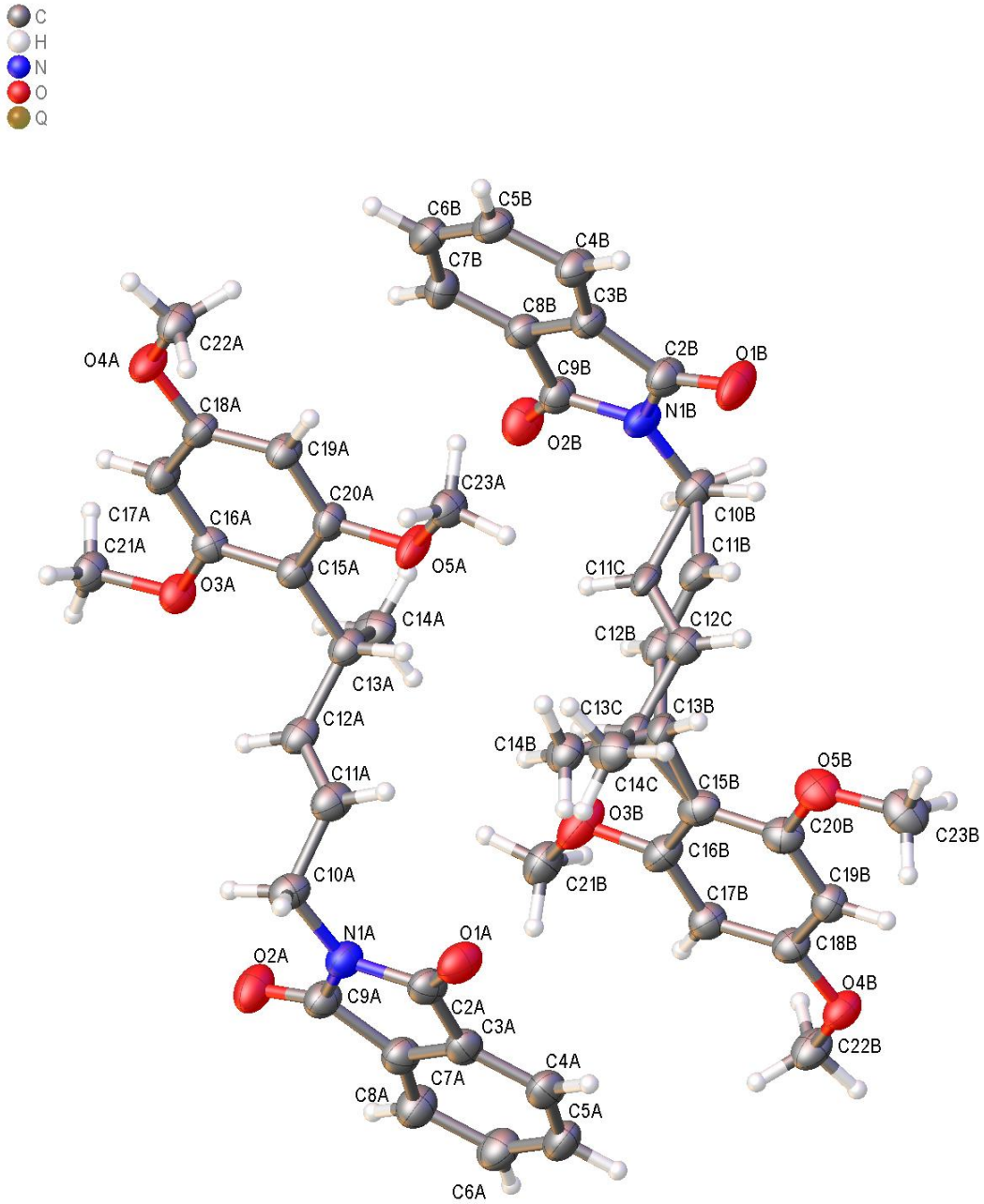
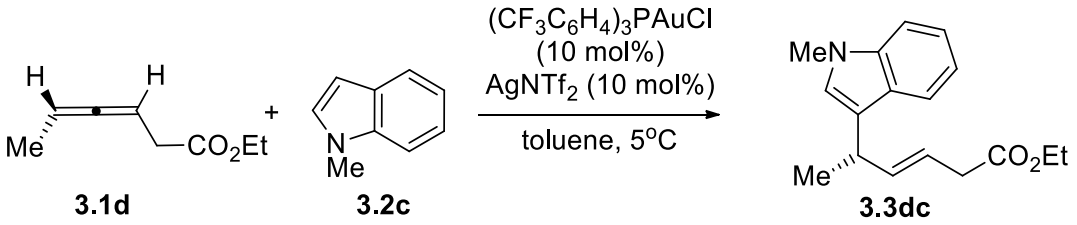


Figure 3.2: X-ray crystal structure of **3.3eb** showing absolute stereochemistry

3.3.4 Investigation into the loss of chirality transfer

In order to better understand why we see reduced chirality transfer for some substrates and nucleophiles, a small study was carried out. It is thought that the reason for any loss of chirality transfer in the hydroarylation reaction is due to gold-catalysed allene racemisation. In order to provide evidence for this proposal, the e.r. of the allene and the product were measured at different time points over the course of the reaction.



3.1d **3.2c** **3.3dc**

Entry	Equiv. indole **3.2c**	Time (hours)	Allene **3.1d** e.r.[a]	Product **3.3dc** e.r.[b]	NMR conv. (%)[c]
1	0	0.25	55:45	-	-
2	0	1	50:50	-	-
3	4	0	95:5	-	-
4	4	0.25	94:6	-	<5%
5	4	1	93:7	92:8	26%
6	4	6	90:10	92:8	56%
7	4	16	87:13	91:9	78%
8	4	24	83:17	90:10	89%

[a] Determined by CSP-GC [b] Determined by CSP-HPLC. [c] Determined by ^{1}H NMR analysis

Table 3.4: Study of the rate of hydroarylation vs. allene racemisation

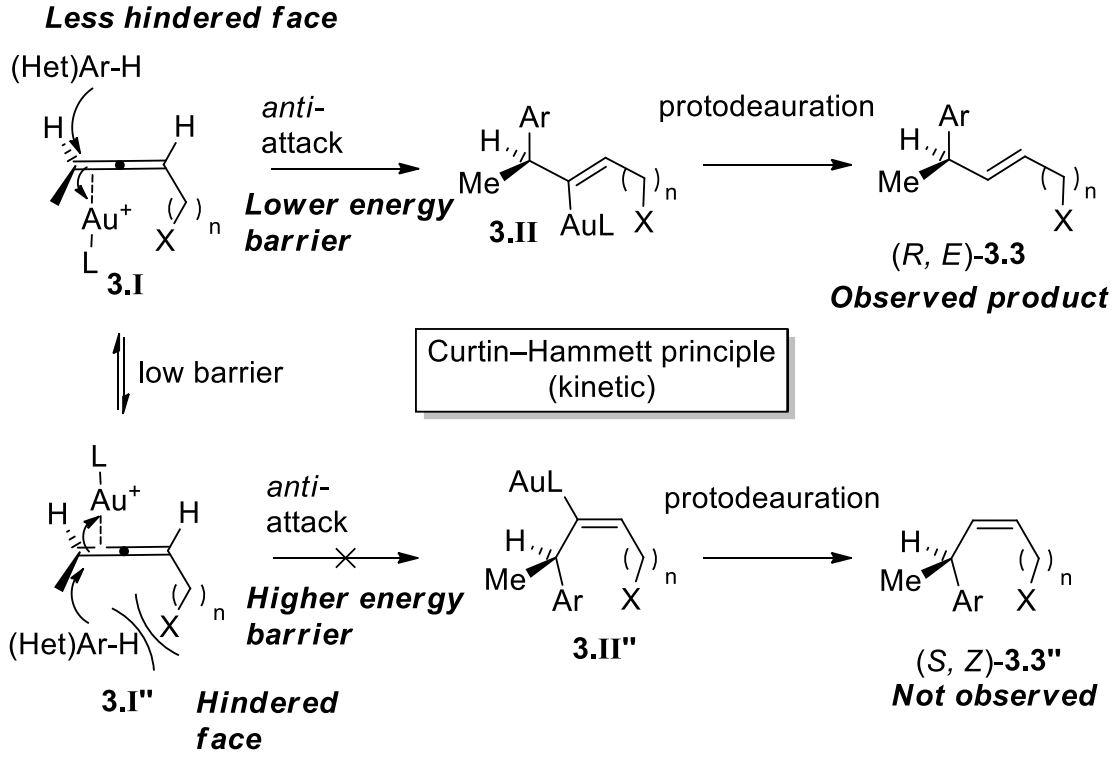
In the absence of indole **3.2c**, allene **3.1d** was almost fully racemised after just 15 minutes and totally racemic within 1 h (Entries 1 and 2, Table 3.4). This shows that gold-catalysed allene racemisation is indeed occurring under our conditions and also suggests that the nucleophile plays a significant role in slowing down allene racemisation (Entries 1 and 2 *vs.* Entries 3 and 4, Table 3.4). This was also the case in the hydroalkoxylation reaction discussed in chapter 2 (see Section 2.3.1) and is thought to be due to the nucleophile reversibly coordinating to the gold catalyst and slowing down its activity.[83, 84] If the properties of the nucleophile affect its ability to coordinate

to the catalyst then this could offer an alternative (or perhaps additional) explanation as to why less electron-rich nucleophiles perform more poorly in terms of chirality transfer.

When indole **3.2c** is present in the reaction mixture, the racemisation of allene **3.1d** is significantly slower than the competing hydroarylation reaction (Entries 3-8, Table 3.4). However, it is clear from the data collected that the allene is slowly racemising under the reaction conditions and this is causing the e.r. of the product to be reduced over time (Entries 3-8, Table 3.4). This suggests that allene racemisation is indeed causing the loss of chirality transfer and that for good chirality transfer to occur, the hydroarylation reaction must outcompete the allene racemisation. This explanation is in keeping with the observed trend (see Section 3.3.3) that less reactive nucleophiles provide poorer chirality transfer.

3.3.5 Proposed mechanism

The hydroarylation reaction is thought to proceed in a similar manner to the hydroalkoxylation reaction previous discussed (Section 2.3.5).



Scheme 3.8: Proposed mechanism of selective hydroarylation of allenes

It is proposed that the gold catalyst can coordinate to either face of the allene, rapidly interconverting between the two intermediates (**3.I** or **3.I''**, Scheme 3.8).[67] Since the face to which the gold catalyst binds is in equilibrium, in accordance with the Curtin-Hammett principle, the energy barrier of the next step of the mechanism defines which product is observed. It is thought that attack of the nucleophile is preferred at the less hindered face of the allene giving selectivity for the observed product (*R, E*)-**3.3** after protodeauration. The product formed through attack at the more hindered face (*S, Z*)-**3.3''** is never detected in our reactions.

3.4 Conclusions

The first intermolecular hydroarylation of 1,3-disubstituted allenes that proceeds with efficient chirality transfer has been developed. To our delight, the reaction is suited to a range of functionalised allenes and tolerates indoles, pyrroles and electron-rich arenes providing products in up to 99% yield, >20:1 positional selectivity and 98:2 e.r. This development is of significance, as previous attempts at achieving chirality transfer in gold-catalysed hydroarylation of allenes gave racemic products.[52] Additionally pyrroles and electron-rich arenes have not previously been reported as suitable nucleophiles for the hydroarylation of 1,3-disubstituted allenes.

Previous attempts at achieving chirality transfer in gold-catalysed hydroarylation of allenes were unsuccessful due to gold-catalysed allene racemisation.[52] This was overcome by developing conditions which allowed the rate of the hydroarylation reaction to outcompete the unwanted gold-catalysed allene racemisation. For the hydroarylation to occur faster than the allene racemisation the substrates and nucleophiles must adhere to certain criteria. Firstly, the enantioenriched allene substrates should contain one inductively withdrawing substituent, this feature of the allene serves two purposes: helping to slow racemisation through destabilisation of the transition state and also ensuring good positional selectivity by electronic differentiation of the π bonds of the allene.

During our studies it was found that the nucleophile used must also meet certain criteria. When more electron-rich nucleophiles such as *N*-Me, *N*-Bn, and unprotected indoles were used, the reaction proceeded with excellent chirality transfer. However, when less electron-rich and thus slower reacting nucleophiles such as *N*-Boc-indole were used, poor chirality transfer was obtained. This supports the proposal that the hydroarylation reaction must outcompete the unwanted gold-catalysed allene racemisation for efficient chirality transfer to occur. It should also be noted that more electron-rich nucleophiles may perform better in terms of chirality transfer by slowing down allene racemisation through stronger reversible coordination to the gold catalyst.

3.5 Experimental

3.5.1 General considerations

^{1}H NMR spectra was recorded on Bruker AV 300 and AV 400 spectrometers at 300 and 400 MHz respectively and referenced to residual solvent. ^{13}C NMR spectra were recorded using the same spectrometers at 75 and 100 MHz respectively. Chemical shift data are quoted in parts per million (ppm) and are referenced to tetramethylsilane (TMS) or to residual solvent peaks ($CDCl_3$ at δ_H 7.26). *J* values are given in Hz and s, d, dd, dt, ddt, dtd, t, td, tt, q, qd, qt, p and m abbreviations correspond to singlet, doublet, doublet of doublet, doublet of triplet, doublet of doublet of triplet, doublet of triplet of doublet, triplet, triplet of doublet, triplet of triplet, quartet, quartet of doublet, quartet of triplet, quintet and multiplet respectively. Mass spectra were obtained at the EPSRC National Mass Spectrometry Service Centre in Swansea. Infrared spectra were obtained on Perkin-Elmer Spectrum 100 FT-IR Universal ATR Sampling Accessory, deposited neat or as a chloroform solution to a diamond/ZnSe plate. Flash column chromatography was carried out using silica gel 60 from Fisher Chemicals or Silicagel 60A from Fluorochem and TLC was performed using Merck silica gel 60 F254 pre-coated sheets and visualised by UV (254 nm) or stained by the use of aqueous acidic $KMnO_4$ or aqueous acidic ceric ammonium molybdate as appropriate. Chemicals were purchased from Sigma-Aldrich, Acros, Apollo Scientific, Fisher, Fluorochem and Manchester Organics chemical companies and used without further purification unless otherwise stated. THF, DCM and DMF were dried using an MBRAUN SPS-800 solvent purification system. Diethyl ether was purified by distilling over CaH_2. High performance liquid chromatography (HPLC) was carried out on Agilent Technologies 1120 Compact LC. Gas chromatography was carried out on a Shimadzu GC2014 with FID.

The gold(I)-catalysed reactions were carried out in screw cap 1 dram vials partially immersed in a bath of IPA cooled by a Huber TC45E-F immersion chiller unless otherwise indicated. No special precautions to exclude air or moisture were taken unless otherwise indicated.

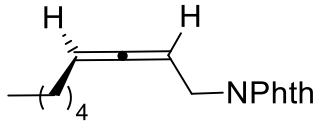
3.5.2 Preparation of allenes

Allenes **3.1d, 3.1e, 3.1g-3.1j, 3.1l-3.1p** were synthesised as described in Section 2.5.3 or purchased (**3.1o**).

(*S*)-Nona-2,3-dien-1-ol, precursor to **3.1f**, was synthesised in the same manner as **2.15** (Section 2.5.2) by Stuart Angiolini.

Allenol precursor to **3.1k** (**2.15**) was synthesised as described in Section 2.5.2

(*S*)-2-(Nona-2,3-dien-1-yl)isoindoline-1,3-dione (3.1f)[60]

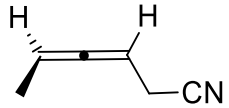


3.1f, 98:2 e.r.

(*S*)-Nona-2,3-dien-1-ol (50.5 mg, 0.60 mmol, 1.0 equiv.), phthalimide (132 mg, 0.90 mmol, 1.5 equiv.) and PPh_3 (236 mg, 0.90 mmol, 1.5 equiv.) in THF (4.8 ml) were stirred at 0 °C. Diisopropyl azodicarboxylate (DIAD) (0.18 ml, 0.90 mmol, 1.5 equiv.) was added dropwise and the reaction mixture was stirred for a further 1 h at 0 °C and then concentrated. The concentrated reaction mixture was loaded directly onto a silica gel column and purified by column chromatography (eluent: 15:1 to 12:1 petrol 40-60 ^{o}C/EtOAc) to give product **3.1f** as a colourless oil (138 mg, 0.51 mmol, 84%, 98:2 e.r.).

R_F 0.32 (12:1 petrol 40-60^{o} C/EtOAc); ν_{max}/cm^{-1} 2927, 2856 (C-H), 1965 (C=C=C), 1711 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89-7.79 (2H, m, Phth), 7.75-7.65 (2H, m, Phth), 5.25-5.13 (2H, m, allene H), 4.27 (2H, app. t, *J* = 4.3 Hz, CH_2N), 1.95-1.80 (2H, m, $C\underline{H}_2CH$), 1.35-1.07 (6H, m, $3CH_2$), 0.81 (3H, t, *J* = 6.8 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8 (C), 167.9 (C), 134.01 (CH), 132.4 (C), 123.4 (CH), 94.8 (CH), 86.9 (CH), 36.8 (CH_2), 31.3 (CH_2), 28.8 (CH_2), 28.6 (CH_2), 22.5 (CH_2), 14.1 (CH_3); Found (TOF MS ASAP+) $[M + H]^+$ 270.1495, $C_{17}H_{20}NO_2$ requires 270.1494; CSP-HPLC (Chiralpak IB, 99.5:0.5 hexane:IPA, 1 ml min^{-1}) (*S*)-**3.1f** 9.9 min and (*R*)-**3.1f** 10.3 min.

(S)-Hexa-3,4-dienenitrile (3.1k)

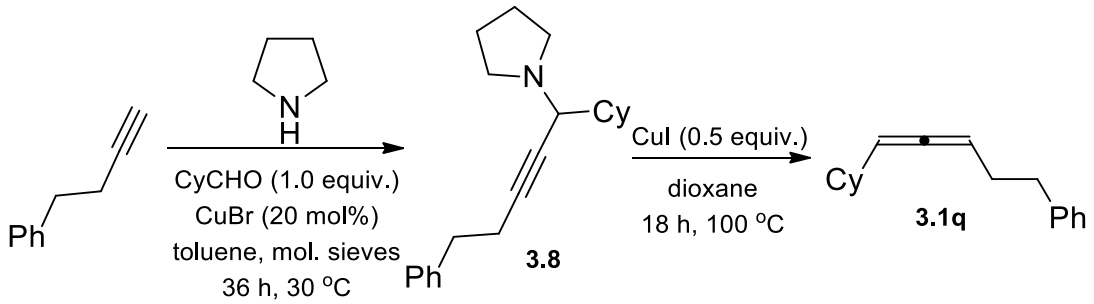


3.1k, 98:2 e.r.

Following procedure reported by Schaus,[85] to a stirred solution of allenol **2.15** (101 mg, 1.20 mmol, 1.0 equiv.) and triphenylphosphine (629 mg, 2.40 mmol, 2.0 equiv.) in Et_2O (12 ml) at 0 °C, DIAD (474 µL, 2.40 mmol, 2.0 equiv.) and then acetone cyanohydrin (219 µL, 2.40 mmol, 2.0 equiv.) were added dropwise. The reaction mixture was stirred at 0 °C for 1 h and then allowed to warm up to room temperature and stirred for a further 24 hours. The solvent was removed under vacuum and the concentrated reaction mixture was loaded directly onto a silica gel column and purified by column chromatography (eluent: 15:1 to 10:1 petrol 40-60 °C/Et_2O) to yield product **3.1k** as a colourless oil (32.3 mg, 0.35 mmol, 29%, 98:2 e.r.).

R_F 0.37 (10:1 petrol 40-60 °C/Et_2O); ν_{max}/cm^{-1} 3019, 2928, 2857 (C-H), 2253 (CN), 1970 (C=C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 5.45-5.54 (1H, m, allene H), 5.13-4.93 (1H, m, allene H), 3.05 (2H, dd, *J* = 6.1, 3.1 Hz, CH_2), 1.71 (3H, dd, *J* = 7.2, 3.1 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.8 (C), 117.8 (C), 90.0 (CH), 81.1 (CH), 18.3 (CH_2), 14.0 (CH_3); $[\alpha]_D^{25\,°C}$ = +19.4 (c = 2.16 in $CHCl_3$); CSP-GC (β-Dex, 100 °C, 35 cm s^{-1}) (*R*)-**3.1k** 6.6 min and (*S*)-**3.1k** 6.7 min.

(5-Cyclohexylpenta-3,4-dien-1-yl)benzene (3.1q)[86]



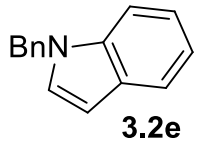
CuBr (226 mg, 20 mol%), pyrrolidine (0.74 ml, 8.9 mmol, 1.0 equiv.) and dry toluene (14 ml) were added to a flask. Distilled cyclohexanecarboxaldehyde (998 mg, 8.9 mmol, 1.0 equiv.), 4 Å molecular sieves (2 g) and 4-phenyl-1-butyne (1.38 ml, 9.8 mmol, 1.1 equiv.) were added to the flask and stirred under Ar at 30 °C for 36 hours. The molecular sieves were removed *via* filtration through a Celite® plug and washed with Et_2O. The crude product was purified by graduated column chromatography (eluent 20:1 petrol 40-60 °C/EtOAc to 10:1 DCM/MeOH - R_f = 0.16 5:1 petrol 40-60 °C/EtOAc) to yield product **3.8** as an impure yellow oil (2.12 g, 7.2 mmol, 81%), which was used directly in the next step. Compound **3.8** (2.07 g, 7.0 mmol, 1.0 equiv.),

anhydrous dioxane (22 ml) and CuI (666 mg, 3.5 mmol, 0.5 equiv.) were added to a flask and heated to reflux for 18 hours. The reaction mixture was cool and concentrated before being loaded directly onto a silica gel column and purified by column chromatography (eluent: hexane) to yield product **3.1q** as a yellow oil (21.7 mg, 0.096 mmol 1%).

R_F 0.48 (hexane); ν_{max}/cm^{-1} 2920, 2848 (C-H), 1959 (C=C=C), 1495, 1447 (C-C Ar); ^1H NMR (300 MHz, $CDCl_3$) δ 7.15-7.25 (3H, m, Ar-H), 7.07-7.15 (2H, m, Ar-H), 5.04-5.13 (1H, m, Allene-H), 4.97-5.04 (1H, m, Allene-H), 2.59-2.70 (2H, m, alkyl-H), 2.17-2.29 (2H, m, alkyl-H), 1.76-1.91 (1H, m, alkyl-H), 1.49-1.68 (5H, m, alkyl-H), 1.07-1.26 (3H, m, alkyl-H), 0.87-1.07 (2H, m, alkyl-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.9 (C), 142.1 (C), 128.7 (CH), 128.4 (CH), 125.9 (CH), 97.7 (CH), 91.3 (CH), 37.4 (CH), 35.7 (CH_2), 33.23 (CH_2), 33.20 (CH_2), 31.0 (CH_2), 26.3 (CH_2), 26.21 (CH_2), 26.20 (CH_2).

3.5.3 Preparation of nucleophiles

1-Benzyl-1H-indole (3.2e)[86]



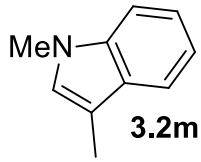
3.2e

Following a procedure reported by Garvey,[87] NaH (60% in oil, 216 mg, 5.4 mmol, 1.08 equiv.) was added portion wise to indole (586 mg, 5.0 mmol, 1.00 equiv.) in DMF (20 mL) at 0 °C. The mixture was stirred at r.t for 45 minutes at r.t before cooling to 0 °C. BnBr (628 µL, 5.25 mmol, 1.05 equiv.) was added dropwise and the solution warmed to r.t and stirred overnight. Water (20 mL) was added and the mixture was extracted with EtOAc (3 x 30mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and then concentrated. The product was purified by column chromatography (eluent: 100:1 to 60:1 petrol 40-60 °C/EtOAc) to yield product **3.2e** as a yellow oil (727 mg, 3.5 mmol, 70%).

R_F 0.34 (60:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 3056, 3028, 2914 (C-H), 1511, 1484, 1463, 1453 (C-C Ar); ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (1H, ddd, *J* = 7.5, 1.5, 0.8 Hz, Ar-H), 7.25-7.16 (4H, m, Ar-H), 7.13-6.99 (5H, m, Ar-H), 6.48 (1H, dd, *J* = 3.2, 0.9 Hz, NCH=C<u>H</u>), 5.25 (2H, s, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7 (C), 136.4 (C), 128.89

(CH), 128.85 (CH), 128.4 (C), 127.7 (CH), 126.9 (CH), 121.8 (CH), 121.1 (CH), 119.7 (CH), 109.8 (CH), 101.8 (CH), 50.2 (CH_2).

1,3-Dimethyl-1H-indole (3.2m)[87]

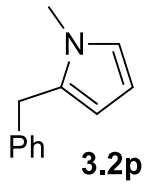


3.2m

NaH (60% in oil, 200 mg, 5.0 mmol, 1.25 equiv.) was added portion wise to 3-methylindole (525 mg, 4.0 mmol, 1.00 equiv.) in DMF (5 mL) at r.t. The mixture was stirred at r.t for 30 minutes at r.t before cooling to 0 °C. MeI (747 µL, 12.0 mmol, 3.00 equiv.) was added in one portion and the solution warmed to r.t and stirred for 5 hours. Water (20 mL) was added and the mixture was extracted with EtOAc (3 x 30mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and then concentrated. The product was purified by column chromatography (eluent: neat to 60:1 petrol 40-60 °C/EtOAc) to yield product **3.2m** as a yellow oil (291 mg, 2.0 mmol, 50%).

R_F 0.66 (20:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 3053, 2915, 2883 (C-H), 1616, 1470 (C-C Ar); ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (1H, d, *J* = 8.3 Hz, Ar-H), 7.32-7.19 (2H, m, Ar-H), 7.15-7.09 (1H, m, Ar-H), 6.84 (1H, s, NCH=C), 3.75 (3H, s, CH_3), 2.35 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.1 (C), 128.8 (C), 126.6 (CH), 121.5 (CH), 119.1 (CH), 118.6 (CH), 110.2 (C), 109.1 (CH), 32.6 (CH_3), 9.7 (CH_3).

2-Benzyl-1-methyl-1H-pyrrole (3.2p)[88]



3.2p

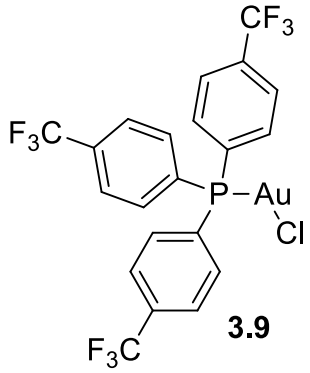
Following procedure reported by Mal'kina,[89] under Schlenk conditions at -78 °C *n*BuLi (2M in cyclohexane, 2.5 mL, 5.0 mmol, 1 equiv.) was added dropwise to *N*-methylpyrrole (311 µL, 5.0 mmol, 1 equiv.) in THF (5 mL). The solution was slowly allowed to warm to r.t and stirred overnight. The mixture was cooled to -78 °C and cooled BnBr (595 µL, 5.0 mmol, 1 equiv.) in THF (5 mL) was added in one portion. The

reaction was slowly warmed to r.t over 1 hour and stirred for a further 5 hours. The reaction was quenched with water, separated and the aqueous layer was extracted twice with Et_2O. After being concentrated the product was purified by column chromatography (eluent: neat to 50:1 petrol 40-60 ^oC/EtOAc) to yield product **3.2p** as a yellow oil (507 mg, 3.0 mmol, 59%). This was used within one day and despite being stored under argon in the freezer turned to a white paste within two weeks.

R_F 0.71 (50:1 petrol 40-60 ^oC/EtOAc); ν_{max}/cm^{-1} 3024, 2899 (C-H), 1604, 1492 (C-C Ar); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.26 (2H, m, Ar-H), 7.24-7.13 (3H, m, Ar-H), 6.58 (1H, dd, *J* = 2.7, 1.9 Hz, pyrrole-H), 6.08 (1H, dd, *J* = 3.5, 2.7 Hz, pyrrole-H), 5.95-5.87 (1H, m, pyrrole-H), 3.95 (2H, s, CH_2), 3.43 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5 (C), 131.4 (C), 128.5 (2xCH), 126.2 (CH), 121.8 (CH), 107.9 (CH), 106.6 (CH), 33.8 (CH_3), 32.9 (CH_2).

3.5.4 Preparation of gold catalyst

$(CF_3C_6H_4)_3PAuCl$ (3.9)[90]



3.9

Thioethanol (860 mg, 7.10 mmol, 3.3 equiv.) in MeOH (5 mL) was added dropwise to $NaAuCl_4.2H_2O$ (850 mg, 2.14 mmol, 1.0 equiv.) in water (3.7 mL) and MeOH (1 7mL) at 0 ^oC. The reaction was stirred at r.t. until the solution changed from yellow to colourless (45 mins). The mixture was cooled to 0 ^oC and $(4\text{-}CF_3C_6H_4)_3P$ (1.00 g, 2.14 mmol, 1 equiv.) in DCM (17mL) and MeOH (11.4 mL) at 0 ^oC was added slowly. The reaction mixture was then warmed to r.t. and stirred overnight. The mixture was cooled and concentrated until a white solid precipitated. The precipitate was filtered off and washed with pentane before being recrystallised twice from DCM/pentane to give the desired product as a white solid **3.9** (1.08 g, 1.54 mmol, 72%).

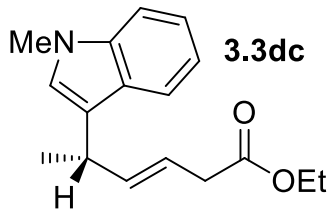
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83-7.76 (6H, m Ar-H), 7.73-7.63 (6H, m, Ar-H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.8 (q, *J* = 33.7 Hz, <u>C</u>CF_3), 134.6 (d, *J* = 14.7 Hz, <u>C</u>HCP), 131.8 (d, *J* = 60.2 Hz, CP), 126.5 (dq, *J* = 11.8, 3.7 Hz, <u>C</u>HCCF_3), 123.1 (q, *J* = 273.3 Hz, CF_3); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.36; ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.98; Found (TOF MS ASAP+) $[M + NH_4]^+$ 716.0240, $C_{21}H_{16}F_9PAuClN$ requires 716.0231.

3.5.5 Gold-catalysed hydroarylation reactions

General procedure

Allene **3.1** (0.15 mmol, 1 equiv.), toluene (0.1 mL) and nucleophile **3.2** (0.6 mmol, 4 equiv.) were added to a 1 dram vial equipped with a small stirrer bar and cooled to 5 °C. Catalyst $(4\text{-}CF_3C_6H_4)_3PAuCl$ (0.015 mmol, 10 mol%) followed by $AgNTf_2$ (0.015 mmol, 10 mol%) were added in quick succession and the reaction was allowed to stir at 5 °C for 3 days. The reaction mixture was then loaded directly onto the column and purified immediately by column chromatography to give product **3.3**. Alternatively, the reaction mixture can be stored in the freezer to prevent further reaction before purification in the same manner. (Filtration through a short plug of silica was found to be insufficient to quench the reaction as the catalyst was found to co-elute with the product and any remaining starting material.)

Ethyl (*S,E*)-5-(1-methyl-1H-indol-3-yl)hex-3-enoate (3.3dc)



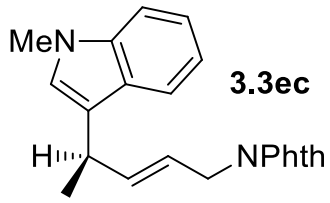
3.3dc

General procedure followed and crude purified by column chromatography (eluent: 20:1 petrol 40-60 °C/EtOAc) to yield product **3.3dc** as a colourless oil (27.3 mg, 0.10 mmol, 67%, 11:1 regioselectivity, 92:8 e.r.).

R_F 0.21 (15:1 hexane/EtOAc); ν_{max}/cm^{-1} 2976 (C-H), 1731 (C=O), 1613, 1470 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (1H, d, *J* = 7.9 Hz, indole), 7.30 (1H, d, *J* = 8.1 Hz, indole), 7.22 (2H, ddd, *J* = 8.1, 6.9, 1.0 Hz, indole), 7.10 (1H, ddd, *J* = 7.9, 6.9, 1.2 Hz, indole), 6.84 (1H, s, NC<u>H</u>=C), 5.82 (1H, dd, *J* = 15.4, 6.6 Hz, =C<u>H</u>CH), 5.69 (1H, dt, *J* = 15.4, 6.6 Hz, =C<u>H</u>CH_2), 4.15 (2H, q, *J* = 7.1 Hz, C<u>H</u>$_2CH_3$), 3.86-3.73 (1H, m, C<u>H</u>CH_3), 3.75 (3H, s,

NCH_3), 3.07 (2H, d, *J* = 6.6 Hz, $CHC\underline{H}_2$), 1.48 (3H, d, *J* = 7.0 Hz, $CHC\underline{H}_3$), 1.27 (3H, t, *J* = 7.0 Hz, $CH_2C\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3 (C), 139.4 (CH), 137.5 (CH), 127.3 (CH), 125.3 (CH), 121.7 (CH), 120.3 (CH), 119.8 (CH), 119.1 (C), 118.7 (CH), 109.3 (CH), 60.6 (CH_2), 38.2 (CH_2), 34.0 (CH), 32.7 (CH_3), 20.8 (CH_3), 14.4 (CH_3); Found (FTMS + p NSI) $[M + H]^+$ 272.1640, $C_{17}H_{22}NO_2$ requires 272.1645; $[\alpha]_D^{22\,°C}$ = -3.8 (c = 0.52 in $CHCl_3$); CSP-HPLC (Chiralcel OD-H, 99.5:0.5 hexane:IPA, 1 ml min^{-1}) (*R*)-**3.3dc** 24.6 min and (*S*)-**3.3dc** 33.0 min.

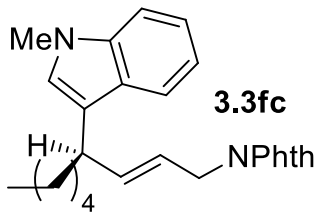
(*R,E*)-2-(4-(1-Methyl-1H-indol-3-yl)pent-2-en-1-yl)isoindoline-1,3-dione (3.3ec)



General procedure followed and crude purified by column chromatography (eluent: 6:1 petrol 40-60 °C/EtOAc) to yield product **3.3ec** as a light yellow oil (48.4 mg, 0.14 mmol, 94%, >20:1 regioselectivity, 97:3 e.r.).

R_F 0.30 (5:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2963, 2928 (C-H), 1708 (C=O), 1613, 1467 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.80 (2H, m, Phth), 7.74-7.67 (2H, m, Phth), 7.57 (1H, d, *J* = 7.9 Hz, indole), 7.27 (1H, m, indole), 7.19 (1H, ddd, *J* = 8.2, 6.9, 1.1 Hz, indole), 7.04 (1H, ddd, *J* = 7.9, 6.9, 1.1 Hz, indole), 6.80 (1H, s, $NC\underline{H}$=C), 6.03 (1H, ddt, *J* = 15.4, 6.6, 1.2 Hz, =$C\underline{H}$CH), 5.62 (1H, dtd, *J* = 15.4, 5.9, 1.3 Hz, =$C\underline{H}CH_2$), 4.28 (2H, d, *J* = 5.9 Hz, CH_2), 3.80-3.69 (1H, m, $C\underline{H}CH_3$), 3.73 (3H, s, NCH_3), 1.42 (3H, d, *J* = 7.0 Hz, $C\underline{H}_3CH$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1 (C), 139.6 (CH), 137.3 (C), 134.0 (CH), 132.3 (C), 127.1 (C), 125.5 (CH), 123.3 (CH), 121.7 (CH), 121.6 (CH), 119.6 (CH), 118.69 (CH), 118.66 (C), 109.3 (CH), 39.7 (CH_2), 33.4 (CH), 32.7 (CH_3), 20.7 (CH_3); Found (FTMS + p NSI) $[M + H]^+$ 345.1598, $C_{22}H_{21}N_2O_2$ requires 345.1598; $[\alpha]_D^{24\,°C}$ = -4.1 (c = 2.95 in EtOH); CSP-HPLC (Chiralpak IB, 99.2:0.8 hexane:IPA, 1 ml min^{-1}) (*R*)-**3.3ec** 22.1 min and (*S*)-**3.3ec** 23.6 min.

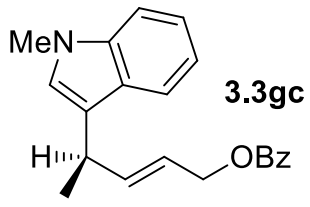
(*R,E*)-2-(4-(1-Methyl-1H-indol-3-yl)nona-2-en-1-yl)isoindoline-1,3-dione (3.3fc)



General procedure followed and crude purified by column chromatography (eluent: 12:1 to 8:1 petrol 40-60 °C/EtOAc) to yield product **3.3fc** as a light yellow oil (48.6 mg, 0.12 mmol, 81%, >20:1 regioselectivity, 98:2 e.r.).

R_F 0.18 (12:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2955, 2928, 2856 (C-H), 1709 (C=O), 1614, 1467 (C-C Ar); ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.89-7.79 (2H, m, Phth), 7.74-7.65 (2H, m, Phth), 7.58 (1H, d, *J* = 8.1 Hz, indole), 7.27 (1H, d, *J* = 8.3 Hz, indole), 7.19 (1H, app. td, *J* = 6.9, 1.0 Hz, indole), 7.04 (1H, app. td, *J* = 7.9, 1.0 Hz, indole), 6.82 (1H, s, NC<u>H</u>=C), 5.99 (1H, dd, *J* = 15.4, 7.7 Hz, =C<u>H</u>CH), 5.62 (1H, dtd, *J* = 15.4, 6.2 Hz, =C<u>H</u>CH_2), 4.27 (2H, d, *J* = 6.2 Hz, =CHC<u>H</u>$_2$), 3.74 (3H, s, NCH_3), 3.55 (1H, app. q, *J* = 7.3 Hz, C<u>H</u>CH_2), 1.95-1.63 (2H, m, CHC<u>H</u>$_2$), 1.38-1.12 (6H, m, $3CH_2$), 0.84 (3H, t, *J* = 6.8 Hz, CH_2C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1 (C), 139.1 (CH), 137.2 (C), 133.9 (CH), 132.4 (CH), 127.3 (C), 125.7 (CH), 123.3 (CH), 122.4 (CH), 121.5 (CH), 119.7 (CH), 118.6 (CH), 117.5 (C), 109.3 (CH), 39.8 (CH_2), 39.7 (CH), 35.3 (CH_2), 32.7 (CH_3), 31.9 (CH_2), 27.4 (CH_2), 22.7 (CH_2), 14.2 (CH_3); Found (TOF MS ASAP+) $[M + H]^+$ 401.2227, $C_{26}H_{29}N_2O_2$ requires 401.2229; $[\alpha]_D^{21\,°C}$ = -7.4 (c = 4.07 in $CHCl_3$); CSP-HPLC (Chiralpak IA, 95:5 hexane:IPA, 1 ml min^{-1}) (*S*)-**3.3fc** 9.3 min and (*R*)-**3.3fc** 10.4 min.

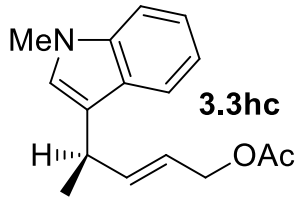
(*R,E*)-4-(1-Methyl-1H-indol-3-yl)pent-2-en-1-yl benzoate (3.3gc)



General procedure followed and crude purified by column chromatography (eluent: 20:1 to 15:1 petrol 40-60 °C/EtOAc) to yield product **3.3gc** as a light yellow oil (45.3 mg, 0.14 mmol, 95%, 15:1 regioselectivity, 97:3 e.r.).

R_F 0.26 (15:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 3055, 2962, 2873 (C-H), 1713 (C=O), 1613, 1471 (C-C Ar); ^{1}H NMR: (300 MHz, $CDCl_3$) δ 8.09 (2H, dd, *J* = 8.3, 1.4 Hz, Ar-H), 7.66 (1H, d, *J* = 7.9 Hz, Ar-H), 7.58 (1H, t, *J* = 7.4 Hz, Ar-H), 7.46 (2H, t, *J* = 7.6 Hz, Ar-H), 7.32 (1H, d, *J* = 8.3 Hz, Ar-H), 7.25 (1H, t, *J* = 7.1 Hz, Ar-H), 7.12 (1H, t, *J* = 7.4 Hz, Ar-H), 6.87 (1H, s, NC<u>H</u>=C), 6.15 (1H, dd, *J* = 15.4, 6.6 Hz, =C<u>H</u>CH), 5.84 (1H, dtd, *J* = 15.4, 6.2, 1.3 Hz, =C<u>H</u>CH_2), 4.84 (2H, d, *J* = 6.2 Hz, OCH_2), 3.85 (1H, app. p, *J* = 7.2 Hz, C<u>H</u>CH_3), 3.77 (2H, s, NCH_3), 1.52 (3H, d, *J* = 7.0 Hz, CHC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1 (C), 140.4 (CH), 136.9 (C), 132.5 (CH), 130.1 (C), 129.3 (CH), 128.0 (CH), 126.7 (C), 125.0 (CH), 121.9 (CH), 121.3 (CH), 119.3 (CH), 118.4 (CH), 118.1 (C), 109.0 (CH), 65.3 (CH_2), 33.3 (CH), 32.3 (CH_3), 20.2 (CH_3); Found (FTMS + p NSI) $[M + H]^+$ 320.1648, $C_{21}H_{21}NO_2$ requires 320.1645; $[\alpha]_D^{23\,°C}$ = -2.0 (c = 2.93 in $CHCl_3$); CSP-HPLC (Chiralpak IB, 98:2 hexane:IPA, 1 ml min^{-1}) (*R*)-**3.3gc** 7.4 min and (*S*)-**3.3gc** 11.8 min.

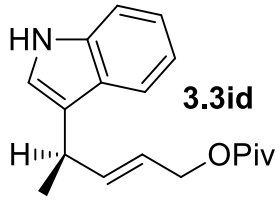
(*R,E*)-4-(1-Methyl-1H-indol-3-yl)pent-2-en-1-yl acetate (3.3hc)



General procedure followed and crude purified by column chromatography (eluent: 15:1 to 12:1 petrol 40-60 °C/EtOAc) to yield product **3.3hc** as a colourless oil (28.5 mg, 0.11 mmol, 74%, 15:1 regioselectivity, 97:3 e.r.).

R_F 0.29 (10:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2929, 2873 (C-H), 1733, (C=O), 1614, 1471 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (1H, d, *J* = 7.9 Hz, indole), 7.22 (1H, d, *J* = 8.2 Hz, indole), 7.23 (1H, ddd, *J* = 8.2, 6.8, 1.1 Hz, indole), 7.10 (1H, ddd, , *J* = 7.9, 6.8, 1.2 Hz, indole), 6.83 (1H, s, NC<u>H</u>=C), 6.03 (1H, ddt, *J* = 15.4, 6.6, 1.1 Hz, =C<u>H</u>CH), 5.68 (1H, dtd, *J* = 15.4, 6.4, 1.3 Hz, =C<u>H</u>CH_2), 4.56 (2H, d, *J* = 6.4 Hz, C<u>H</u>$_2$HC=), 3.91-3.72 (1H, m, C<u>H</u>CH_3), 3.76 (3H, s, NCH_3), 2.06 (3H, s, O=CCH_3), 1.48 (3H, d, *J* = 7.0 Hz, C<u>H</u>$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0 (C), 140.7 (CH), 137.4 (C), 127.1 (C), 125.4 (CH), 122.3 (CH), 121.7 (CH), 119.6 (CH), 118.8 (CH), 118.5 (C), 109.4 (CH), 65.3 (CH_2), 33.7 (CH), 32.8 (CH_3), 21.2 (CH_3), 20.6 (CH_3); Found (TOF MS ASAP+) $[M + H]^+$ 258.1494, $C_{16}H_{20}NO_2$ requires 258.1491; $[\alpha]_D^{23\,°C}$ = -7.0 (c = 1.43 in EtOH); CSP-HPLC (Chiralpak, 99.6:0.4 hexane:IPA, 1 ml min^{-1}) (*R*)-**3.3hc** 11.5 min and (*S*)-**3.3hc** 12.3 min.

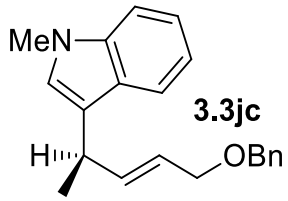
(*R,E*)-4-(1H-Indol-3-yl)pent-2-en-1-yl pivalate (3.3id)



General procedure followed and crude purified by column chromatography (eluent: 15:1 to 12:1 petrol 40-60 °C/EtOAc) to yield product **3.3id** as a colourless oil (24.8 mg, 0.09 mmol, 58%, 8:1 regioselectivity, 94:6 e.r.).

R_F 0.21 (12:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 3411 (N-H), 2968, 2932, 2872 (C-H), 1709 (C=O), 1479, 1456 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (1H, bs, NH), 7.63 (1H, d, *J* = 7.9 Hz, indole), 7.36 (1H, d, *J* = 8.1 Hz, indole), 7.20 (1H, ddd, *J* = 8.1, 7.1, 1.1 Hz, indole), 7.10 (1H, ddd, *J* = 7.9, 7.1, 0.9 Hz, indole), 6.97 (1H, d, *J* = 2.2 Hz, NC<u>H</u>=C), 6.01 (1H, ddt, *J* = 15.2, 6.8, 1.2 Hz, =C<u>H</u>CH), 5.69 (1H, dtd, *J* = 15.2, 6.2, 1.1 Hz, =C<u>H</u>CH_2), 4.59 (2H, d, *J* = 6.2 Hz, C<u>H</u>$_2$HC=), 3.80 (1H, p, *J* = 6.8 Hz, C<u>H</u>CH_3), 1.49 (3H, d, *J* = 7.0 Hz, C<u>H</u>$_3$CH), 1.22 (9H, s, 3CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5 (C), 140.0 (CH), 136.7 (C), 126.8 (C), 122.8 (CH), 122.1 (CH), 120.5 (CH), 120.1 (C), 119.7 (CH), 119.3 (CH), 111.3 (CH), 65.1 (CH_2), 38.9 (C), 33.8 (CH), 27.4 (CH_3), 20.5(CH_3); Found (FTMS + p NSI) $[M + H]^+$ 286.1803, $C_{18}H_{24}NO_2$ requires 286.1802; $[\alpha]_D^{22\,°C}$ = -11.9 (c = 1.01 in $CHCl_3$); CSP-HPLC (Chiralpak IA, 99:1 hexane:IPA, 1 ml min^{-1}) (*S*)-**3.3id** 41.8 min and (*R*)-**3.3id** 51.7 min.

(*R,E*)-3-(5-(Benzyloxy)pent-3-en-2-yl)-1-methyl-1H-indole (3.3jc)

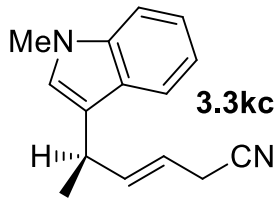


General procedure followed and crude purified by column chromatography (eluent: 20:1 petrol 40-60 °C/EtOAc) to yield product **3.3jc** as a colourless oil (33.9 mg, 0.11 mmol, 74%, 6:1 regioselectivity, 85:15 e.r.).

R_F 0.35 (15:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 3027, 2961, 2928, 2852 (C-H), 1614, 1471 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (1H, d, *J* = 8.0 Hz, indole), 7.41-7.20

(7H, m, indole + Ar-H), 7.16-7.06 (1H, m, indole), 6.85 (1H, s, NC<u>H</u>=C), 6.00 (1H, ddt, *J* = 15.4, 6.7, 1.3 Hz, =C<u>H</u>CH), 5.74 (1H, dtd, *J* = 15.4, 6.2, 1.3 Hz, =C<u>H</u>CH_2), 4.52 (2H, s, CH_2Ph), 4.05 (2H, d, *J* = 6.2 Hz, =CHC<u>H_2</u>), 3.91-3.75 (1H, m, C<u>H</u>CH_3), 3.76 (3H, s, NCH_3), 1.51 (3H, d, *J* = 7.0 Hz, C<u>H</u>CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4 (CH), 138.6 (C), 137.4 (C), 128.5 (CH), 127.9 (CH), 127.6 (CH), 127.2 (C), 125.3 (CH), 124.7 (CH), 121.6 (CH), 119.7 (CH), 118.9 (C), 118.7 (CH), 109.3 (CH), 72.0 (CH_2), 71.0 (CH_2), 33.7 (CH), 32.7 (CH_3), 20.8 (CH_3); Found (TOF MS ASAP+) $[M + H]^+$ 306.1857, $C_{21}H_{25}NO$ requires 306.1858; $[\alpha]_D^{24\ ℃}$ = -20.9 (c = 2.68 in $CHCl_3$ CSP-HPLC (Chiralcel OD-H, 99:1 hexane:IPA, 1 ml min^{-1}) (*R*)-**3.3jc** 17.1 min and (*S*)-**3.3jc** 21.1 min.

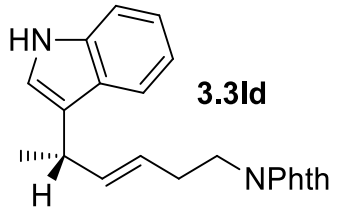
(*R,E*)-5-(1-Methyl-1H-indol-3-yl)hex-3-enenitrile (3.3kc)



General procedure followed and crude purified by column chromatography (eluent: 12:1 petrol 40-60 °C/EtOAc) to yield product **3.3kc** as a yellow oil (26.0 mg, 0.12 mmol, 77%, >20:1 regioselectivity, 98:2 e.r.).

R_F 0.16 (12:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 3018, 2963, 2930, 2873 (C-H), 2250 (CN), 1613, 1471 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (1H, dt, *J* = 7.9, 1.0 Hz, indole), 7.31 (1H, dt, *J* = 8.3, 1.0 Hz, indole), 7.28-7.20 (1H, m, indole), 7.11 (1H, ddd, *J* = 7.9, 6.9, 1.2 Hz, indole), 6.85 (1H, s, NC<u>H</u>=C), 6.09 (1H, ddt, *J* = 15.3, 6.7, 1.6 Hz, =C<u>H</u>CH), 5.42 (1H, dtd, *J* = 15.3, 5.6, 1.4 Hz, =C<u>H</u>CH_2), 3.82 (1H, app. p, *J* = 7.0 Hz, C<u>H</u>CH_3), 3.76 (3H, s, NCH_3), 3.07 (2H, app. dt, *J* = 5.6, 1.4 Hz, CHC<u>H_2</u>), 1.48 (3H, d, *J* = 7.0 Hz, CHC<u>H_3</u>); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.9 (CH), 137.3 (C), 127.0 (C), 125.4 (CH), 121.8 (CH), 119.5 (CH), 118.9 (CH), 118.00 (C), 117.98 (C), 115.9 (CH), 109.4 (CH), 33.7 (CH), 32.7 (CH_3), 20.6 (CH_3), 20.4 (CH_2); Found (TOF MS ASAP+) $[M + H]^+$ 225.1391, $C_{16}H_{17}N_2$ requires 225.1392; $[\alpha]_D^{22\ ℃}$ = +7.2 (c = 1.66 in $CHCl_3$); CSP-HPLC (Chiralpak IB, 99:1 hexane:IPA, 1 ml min^{-1}) (*S*)-**3.3kc** 24.7 min and (*R*)-**3.3kc** 32.3 min.

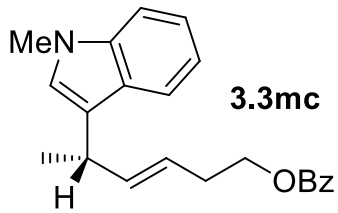
(*S,E*)-2-(5-(1H-Indol-3-yl)hex-3-en-1-yl)isoindoline-1,3-dione (3.3ld)



General procedure followed and crude purified by column chromatography (eluent: 10:1 to 5:1 petrol 40-60 °C/EtOAc) to yield product **3.3ld** as a light yellow oil (49.8 mg, 0.14 mmol, 97%, 11:1 regioselectivity, 76:24 e.r.).

R_F 0.21 (5:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 3413 (N-H), 3019, 2966 (C-H), 1706 (C=O), 1617, 1456 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (1H, br s, NH), 7.85-7.76 (2H, m, Phth), 7.73-7.63 (2H, m, Phth), 7.56 (1H, d, *J* = 7.9 Hz, indole), 7.31 (1H, d, *J* = 8.1 Hz, indole), 7.15 (2H, ddd, *J* = 8.1, 7.1, 1.2 Hz, indole), 7.09-6.97 (1H, m, indole), 6.85 (1H, d, *J* = 2.4 Hz, NC<u>H</u>=C), 5.72 (1H, ddt, *J* = 15.3, 6.9, 1.2 Hz, =C<u>H</u>CH), 5.53 (1H, dtd, *J* = 15.3, 6.9, 1.1 Hz, =C<u>H</u>CH_2), 3.75 (2H, t, *J* = 7.1 Hz, CH_2N), 3.66 (1H, m, C<u>H</u>CH_3), 2.42 (2H, q, *J* = 7.0 Hz, CHC<u>H</u>$_2$), 1.34 (3H, d, *J* = 7.0 Hz, CHC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5 (C), 138.5 (CH), 136.6 (C), 133.9 (CH), 132.2 (C), 126.8 (C), 124.3 (CH), 123.2 (CH), 121.9 (CH), 120.6 (C), 120.2 (CH), 119.6 (CH), 119.2 (CH), 111.2 (CH), 37.9 (CH_2), 33.9 (CH), 31.6 (CH_2), 20.8 (CH_3); Found (TOF MS ASAP+) $[M + H]^+$ 345.1599, $C_{22}H_{20}N_2O_2$ requires 345.1603; $[\alpha]_D^{21\,℃}$ = -3.2 (c = 3.71 in $CHCl_3$); CSP-HPLC (Chiralpak IA, 95:5 hexane:IPA, 1 ml min^{-1}) (*S*)-**3.3ld** 51.4 min and (*R*)-**3.3ld** 61.9 min.

(*S,E*)-5-(1-Methyl-1H-indol-3-yl)hex-3-en-1-yl benzoate (3.3mc)

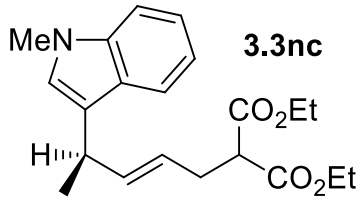


General procedure followed and crude purified by column chromatography (eluent: 50:1 petrol 40-60 °C/EtOAc) to yield product **3.3mc** as a colourless oil (42.3 mg, 0.12 mmol, 82%, 7:1 regioselectivity, 92:8 e.r.).

R_F 0.24 (30:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 3022, 2961, 2929 (C-H), 1714 (C=O), 1613, 1602, 1470 (C-C Ar); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (2H, d, *J* = 7.9 Hz, Ar-H), 7.65 (1H, d, *J* = 7.9 Hz, indole), 7.57 (1H, t, *J* = 7.4 Hz, Ar-H), 7.43 (2H, t, *J* = 7.8 Hz, Ar-

H), 7.30 (1H, d, *J* = 8.2 Hz, indole), 7.23 (1H, m, indole), 7.08 (1H, ddd, *J* = 7.9, 6.9, 0.9 Hz, indole), 6.81 (1H, s, NC<u>H</u>=C), 5.86 (1H, dd, *J* = 15.3, 7.0 Hz, =C<u>H</u>CH), 5.63 (1H, dt, *J* = 15.3, 7.3 Hz, =C<u>H</u>CH_2), 4.38 (2H, td, *J* = 6.7, 2.2 Hz, OCH_2), 3.84-3.75 (1H, m, C<u>H</u>CH_3), 3.71 (3H, s, NCH_3), 2.53 (2H, app. q, *J* = 6.7 Hz, CHC<u>H</u>$_2$), 1.46 (1H, d, *J* = 7.0 Hz, CHC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7 (C), 138.4 (CH), 137.4 (C), 132.9 (CH), 130.6 (C), 129.7 (CH), 128.4 (CH), 127.2 (C), 125.2 (CH), 123.7 (CH), 121.6 (CH), 119.7 (CH), 119.3 (C), 118.7 (CH), 109.3 (CH), 64.6 (CH_2), 34.1 (CH_3), 32.7 (CH), 32.1 (CH_2), 21.0 (CH_3); Found (FTMS + p NSI) $[M + H]^+$ 334.1802, $C_{22}H_{24}NO_2$ requires 334.1804; $[\alpha]_D^{21\,°C}$ = +2.2 (c = 2.71 in $CHCl_3$); CSP-HPLC (Chiralpak IB, 99.6:0.4 hexane:IPA, 1 ml min^{-1}) (*S*)-**3.3mc** 20.6 min and (*R*)-**3.3mc** 62.0 min.

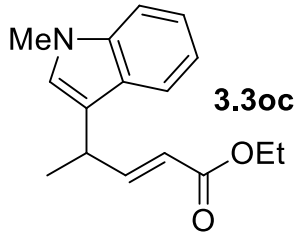
Diethyl (*R,E*)-2-(4-(1-methyl-1H-indol-3-yl)pent-2-en-1-yl)malonate (3.3nc)



General procedure followed and crude purified by column chromatography (eluent: 20:1 petrol 40-60 °C/EtOAc) to yield product **3.3nc** as a colourless oil (52.1 mg, 0.14 mmol, 96%, 18:1 regioselectivity, 87:13 e.r.).

R_F 0.28 (10:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2962, 2929, 2871 (C-H), 1729 (C=O), 1614, 1469 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (1H, dt, *J* = 7.9, 1.0 Hz, indole), 7.28 (1H, m, indole), 7.20 (1H, ddd, *J* = 8.2, 6.9, 1.2 Hz, indole), 7.07 (1H, ddd, *J* = 7.9, 6.9, 1.2 Hz, indole), 6.79 (1H, s, NC<u>H</u>=C), 5.78 (1H, ddt, *J* = 15.3, 7.0, 1.2 Hz, =C<u>H</u>CH), 5.51 (1H, dtd, *J* = 15.3, 6.9, 1.2 Hz, =C<u>H</u>CH_2), 4.15 (4H, m, 2C<u>H</u>$_2$$CH_3$), 3.74 (3H, s, NCH_3), 3.69 (2H, m, C<u>H</u>CH_3), 3.39 (1H, t, *J* = 7.6 Hz, C<u>H</u>CH_2), 2.62 (2H, app. t, *J* = 7.3 Hz, =CHC<u>H</u>$_2$), 1.41 (3H, d, *J* = 7.0 Hz, CHC<u>H</u>$_3$), 1.23 (6H, q, *J* = 7.7 Hz, 2CH_2C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.23 (C), 169.19 (C), 138.7 (CH), 137.4 (C), 127.2 (C), 125.2 (CH), 123.8 (CH), 121.6 (CH), 119.8 (CH), 119.2 (C), 118.7 (CH), 109.3 (CH), 61.4 (CH_2), 52.5 (CH), 34.0 (CH), 32.7 (CH_3), 31.9 (CH_2), 21.0 (CH_3), 14.23 (CH_3), 14.19 (CH_3); Found (TOF MS ASAP+) $[M + H]^+$ 358.2014, $C_{21}H_{28}NO_4$ requires 358.2014; $[\alpha]_D^{24\,°C}$ = -4.0 (c = 3.96 in $CHCl_3$); CSP-HPLC (Chiralpak IB, 98:2 hexane:IPA, 1 ml min^{-1}) (*S*)-**3.3nc** 9.7 min and (*R*)-**3.3nc** 10.5 min.

Ethyl (*E*)-4-(1-methyl-1H-indol-3-yl)pent-2-enoate (3.3oc)

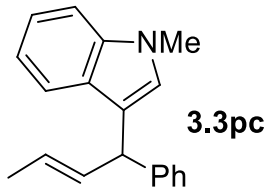


3.3oc

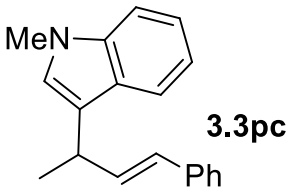
General procedure followed but carried out at r.t and crude purified by column chromatography (eluent: 15:1 petrol 40-60 °C/EtOAc) to yield product **3.3oc** as a colourless oil (8.9 mg, 0.03 mmol, 23%, >20:1 regioselectivity).

R_F 0.21 (15:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2973, 2931 (C-H), 1711 (C=O), 1649, 1471 (C-C Ar); ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (1H, dt, *J* = 8.0, 1.0 Hz, indole), 7.23 (1H, d, *J* = 8.2 Hz, indole), 7.18-7.12 (1H, m, indole), 7.10 (1H, dd, *J* = 15.6, 6.8 Hz, =C<u>H</u>CH), 7.02 (2H, ddd, *J* = 8.0, 6.9, 1.2 Hz, indole), 6.78 (1H, s, NC<u>H</u>=C), 5.79 (1H, dd, *J* = 15.6, 1.5 Hz, =C<u>H</u>C=O), 4.09 (2H, q, *J* = 7.1 Hz, OCH_2), 3.84 (1H, app. p, *J* = 7.0 Hz, C<u>H</u>CH_3), 3.68 (3H, s, NCH_3), 1.43 (3H, d, *J* = 7.0 Hz, CH_3), 1.19 (3H, t, *J* = 7.1 Hz, $CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2 (C), 153.1 (CH), 137.3 (C), 127.0 (C), 125.7 (CH), 121.9 (CH), 119.7 (CH), 119.4 (CH), 119.1 (CH), 116.8 (C), 109.5 (CH), 60.3 (CH_2), 33.7 (CH), 32.8 (CH_3), 19.9 (CH_3), 14.4 (CH_3); Found (FTMS + p NSI) $[M + H]^+$ 258.1489, $C_{16}H_{20}NO_2$ requires 258.1489.

(*E*)-1-Methyl-3-(1-phenylbut-2-en-1-yl)-1H-indole (3.3pc') + (*E*)-1-Methyl-3-(4-phenylbut-3-en-2-yl)-1H-indole (3.3pc)



3.3pc



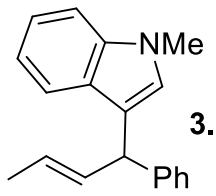
3.3pc

General procedure followed and crude purified by column chromatography (eluent: 10:1 to 5:1 petrol 40-60 °C/toluene) to yield product **3.3pc'** and **3.3pc** as a yellow oil (32.1 mg, 0.12 mmol, 82%, 3:1 regioselectivity, 79:21 e.r. **3.3pc'** and 53:47 e.r. **3.3pc**).

ν_{max}/cm^{-1} 3056, 3024, 2915, 2854 (C-H), 1613, 1546, 1483 (C-C Ar); Found (TOF MS ASAP+) $[M + H]^+$ 262.1596, $C_{19}H_{20}N$ requires 262.1595;

Partial separation of the two other isomers was achieved by further column chromatograph (eluent: 10:1 to 5:1 petrol 40-60 °C/toluene).

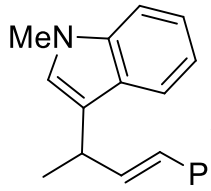
(*E*)-1-Methyl-3-(1-phenylbut-2-en-1-yl)-1H-indole (3.3pc')



3.3pc

R_F 0.36 (5:1 petrol 40-60 °C/toluene); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (1H, dd, *J* = 8.0, 1.0 Hz, indole), 7.35-7.27 (5H, m, Ar-H), 7.28-7.15 (1H, m, indole), 7.03 (1H, ddd, *J* = 8.0, 6.9, 1.1 Hz, indole), 6.74 (1H, s, NC<u>H</u>=C), 5.99 (1H, ddq, *J* = 15.1, 7.5, 1.2 Hz, =C<u>H</u>CH), 5.58 (1H, dqd, *J* = 15.1, 6.5, 1.1 Hz, =CHCH$_3$), 4.92 (1H, d, *J* = 7.5 Hz,=CHC<u>H</u>), 3.75 (3H, s, NCH$_3$), 1.75 (3H, d, *J* = 6.5 Hz, CHC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5 (C), 137.5 (C), 133.7 (CH), 128.42 (CH), 128.39 (CH), 127.4 (C), 127.2 (CH), 126.2 (CH), 125.9 (CH), 121.6 (CH), 120.1 (CH), 118.8 (CH), 117.9 (C), 109.2 (CH), 46.2 (CH), 32.8 (CH$_3$), 18.1 (CH$_3$); $[\alpha]_D^{22\,℃}$ = -7.8 (c = 1.53 in $CHCl_3$); CSP-HPLC (Chiralpak IB, hexane, 1 ml min^{-1}) (*minor*)-**3.3pc'** 26.8 min and (*major*)-**3.3pc'** 35.3 min.

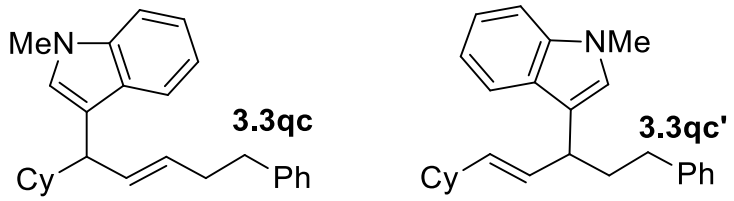
(*E*)-1-Methyl-3-(4-phenylbut-3-en-2-yl)-1H-indole (3.3pc)



3.3pc

R_F 0.31 (5:1 petrol 40-60 °C/toluene); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (1H, dt, *J* = 7.9, 0.9 Hz, indole), 7.39-7.14 (7H, m, Ar-H + indole), 7.07 (1H, ddd, *J* = 8.0, 6.9, 1.1 Hz, indole), 6.88 (1H, s, NC<u>H</u>=C), 6.52 (1H, d, *J* = 15.9 Hz, =CHPh), 6.44 (1H, dd, *J* = 15.9, 5.5 Hz, =C<u>H</u>CH), 3.93 (1H, app. p, *J* = 6.4 Hz, C<u>H</u>CH$_3$), 3.76 (3H, s, NCH$_3$), 1.56 (3H, d, *J* = 7.0 Hz, CHC<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8 (C), 137.3 (C), 135.6 (CH), 128.4 (CH), 128.1 (CH), 127.2 (C), 126.8 (CH), 126.1 (CH), 125.3 (CH), 121.5 (CH), 119.7 (CH), 119.0 (C), 118.7 (CH), 109.2 (CH), 34.2 (CH), 32.6 (CH$_3$), 20.9 (CH$_3$); CSP-HPLC (Chiralpak IB, 99.75:0.25 hexane:IPA, 1 ml min^{-1}) (*R*)-**3.3pc** 13.4 min and (*S*)-**3.3pc** 15.5 min.

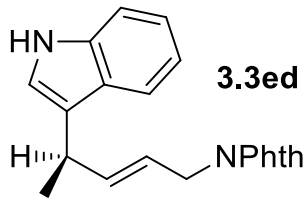
(E)-3-(1-cyclohexyl-5-phenylpent-2-en-1-yl)-1-methyl-1H-indole (3.3qc) + (E)-3-(1-cyclohexyl-5-phenylpent-1-en-3-yl)-1-methyl-1H-indole (3.3qc')



General procedure followed on a reduced scale (0.096 mmol allene **1o**) and crude product purified by column chromatography (eluent: 20:1 to 5:1 petrol 40-60 ^{o}C/toluene) to yield an inseparable mixture of isomers **3.3qc** and **3.3qc'** as a colourless oil (9.7 mg, 0.027 mmol, 28%, 1.4:1 **3.3qc:3.3qc'**).

R_F 0.60 (50:1 petrol 40-60 ^{o}C/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.58 (1 H + 1 H', m, indole major + minor), 7.31 – 7.26 (3 H, m), 7.25 – 7.14 (8 H, m), 7.12 – 7.04 (2 H, m), 6.83 (1 H', s, indole minor), 6.74 (1 H, s, indole major), 5.70 (1 H, ddt, *J* = 15.1, 9.1, 1.3 Hz, =C<u>H</u>CH major), 5.57 – 5.54 (2 H', m, 2=CH minor), 5.50 (1 H, dt, *J* = 15.1, 6.8 Hz, =C<u>H</u>CH_2 major), 3.75 (3 H', s, NCH_3 minor), 3.74 (3 H, s, NCH_3 major), 3.52 (1 H', qm, *J* = 6.8 Hz, =CHC<u>H</u>CH_2 minor), 3.26 (1 H, app. t, *J* = 8.5 Hz, =CHC<u>H</u>Cy major), 2.79 – 2.57 (2 H + 2 H', m, CH_2Ph major + minor), 2.34 (2 H, app. q, *J* = 6.8 Hz, =CHC<u>H</u>$_2CH_2$ major), 2.27 – 2.13 (1 H', m, =CHC<u>H</u>2CH_2 minor), 2.09 – 1.92 (2 H', m, CHC<u>H</u>$_2CH_2$ minor), 1.86 – 1.55 (7 H + 6H', m, Alkyl CHs major + minor), 1.37 – 1.02 (4 H + 4H', m, Alkyl CHs major + minor).

(*R,E*)-2-(4-(1H-Indol-3-yl)pent-2-en-1-yl)isoindoline-1,3-dione (3.3ed)

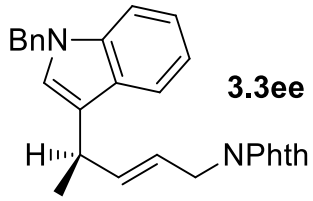


General procedure followed and crude purified by column chromatography (eluent: 5:1 to 4:1 petrol 40-60 ^{o}C/EtOAc) to yield product **3.3ed** as a light yellow oil (44.2 mg, 0.13 mmol, 89%, >20:1 regioselectivity, 95:5 e.r.).

R_F 0.21 (4:1 petrol 40-60 ^{o}C/EtOAc); ν_{max}/cm^{-1} 3409 (br, N-H) 3017, 2966 (C-H), 1705 (C=O), 1615, 1456 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (1H, br s, NH), 7.88-7.80

(2H, m, Phth), 7.74-7.67 (2H, m, Phth), 7.59 (1H, d, *J* = 7.9 Hz, indole), 7.33 (1H, d, *J* = 8.1 Hz, indole), 7.16 (1H, ddd, *J* = 8.1, 6.9, 1.1 Hz, indole), 7.05 (1H, ddd, *J* = 7.9, 6.9, 1.1 Hz, indole), 6.94 (1H, d, *J* = 2.3 Hz, NC<u>H</u>=C), 6.04 (1H, ddt, *J* = 15.4, 6.6, 1.2 Hz, =C<u>H</u>CH), 5.62 (1H, dtd, *J* = 15.4, 5.9, 1.3 Hz, =C<u>H</u>CH_2), 4.29 (2H, d, *J* = 5.9 Hz, CH_2), 3.79 (1H, m, C<u>H</u>CH_3), 1.43 (3H, d, *J* = 7.0 Hz, C<u>H</u>$_3$CH); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 168.2 (C), 139.5 (CH), 136.7 (C), 134.1 (CH), 132.4 (C), 126.8 (C), 123.4 (CH), 122.1 (CH), 121.9 (CH), 120.7 (CH), 120.4 (C), 119.7 (CH), 119.4 (CH), 111.3 (CH), 39.8 (CH_2), 33.6 (CH), 20.6 (CH_3); Found (FTMS + p NSI) $[M + H]^+$ 331.1447, $C_{21}H_{19}N_2O_2$ requires 331.1441; $[\alpha]_D^{25\,^\circ C}$ = -2.2 (c = 3.68 in $CHCl_3$); CSP-HPLC (Chiralpak IB, 12:1 hexane:IPA, 1 ml min^{-1}) (*R*)-**3.3ed** 28.0 min and (*S*)-**3.3ed** 30.0 min.

(*R,E*)-2-(4-(1-Benzyl-1H-indol-3-yl)pent-2-en-1-yl)isoindoline-1,3-dione (3.3ee)

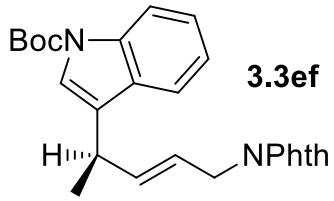


3.3ee

General procedure followed and crude purified by column chromatography (eluent: 10:1 to 8:1 petrol 40-60 °C/EtOAc) to yield product **3.3ee** as a yellow oil (62.8 mg, 0.15 mmol, 99%, >20:1 regioselectivity, 95:5 e.r.).

R_F 0.27 (8:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2965, 2928 (C-H), 1709 (C=O), 1612, 1467 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89-7.81 (2H, m, Phth), 7.74-7.66 (2H, m, Phth), 7.63 (1H, d, *J* = 7.9 Hz, indole), 7.35-7.22 (4H, m, indole + Ph), 7.20-7.01 (4H, m, indole + Ph), 6.92 (1H, s, NC<u>H</u>=C), 6.07 (1H, dd, *J* = 15.4, 6.6 Hz, =C<u>H</u>CH), 5.66 (1H, dt, *J* = 15.4, 6.3 Hz, =C<u>H</u>CH_2), 5.28 (2H, s, C<u>H</u>$_2$Ph), 4.31 (2H, d, *J* = 6.3 Hz, C<u>H</u>$_2$HC=), 3.79 (1H, m, C<u>H</u>CH_3), 1.46 (3H, d, *J* = 7.0 Hz, CHC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2 (C), 139.7 (CH), 137.9 (C), 137.0 (C), 134.0 (CH), 132.4 (C), 128.9 (CH), 127.7 (CH), 127.5 (C), 126.9 (CH), 125.0 (CH), 123.4 (CH), 121.9 (2CH), 119.9 (CH), 119.4 (C), 119.0 (CH), 109.9 (CH), 50.1 (CH_2), 39.8 (CH_2), 33.6 (CH), 20.7 (CH_3); Found (FTMS + p NSI) $[M + H]^+$ 421.1909, $C_{28}H_{25}N_2O_2$ requires 421.1911; $[\alpha]_D^{24\,^\circ C}$ = -4.2 (c = 4.30 in $CHCl_3$); CSP-HPLC (Chiralpak IC, 98:2 hexane:IPA, 1 ml min^{-1}) (*R*)-**3.3ee** 29.3 min and (*S*)-**3.3ee** 32.9 min.

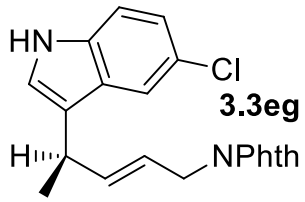
(*R,E*)-*tert*-Butyl 3-(5-(1,3-dioxoisoindolin-2-yl)pent-3-en-2-yl)-1H-indole-1-carboxylate (3.3ef)



General procedure followed and crude purified by column chromatography (eluent: 12:1 to 10:1 petrol 40-60 °C/EtOAc) to yield product **3.3ef** as a light yellow oil (20.8 mg, 0.05 mmol, 32%, 18:1 regioselectivity, 55:45 e.r.).

R_F 0.20 (10:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2975, 2931 (C-H), 1711 (C=O), 1613, 1452 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (1H, d, indole), 7.89-7.80 (2H, m, Phth), 7.76-7.65 (2H, m, Phth), 7.49 (1H, d, *J* = 7.8 Hz, indole), 7.32 (1H, s, indole), 7.30-7.23 (1H, m, indole), 7.15 (1H, ddd, *J* = 7.8, 7.6, 1.0 Hz, indole), 5.99 (1H, ddt, *J* = 15.4, 6.5, 1.2 Hz, =C<u>H</u>CH), 5.61 (1H, dtd, *J* = 15.4, 6.2, 1.3 Hz, =C<u>H</u>CH_2), 4.28 (2H, d, *J* = 6.2 Hz, CH_2), 3.67 (1H, m, C<u>H</u>CH_3), 1.67 (9H, s, $3CH_3$), 1.42 (3H, d, *J* = 7.0 Hz, C<u>H</u>$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1 (C), 150.0 (C), 138.4 (CH), 135.9 (C), 134.1 (CH), 132.4 (C), 130.0 (C), 124.5 (C), 124.4 (CH), 123.4 (CH), 122.9 (CH), 122.4 (CH), 122.1 (CH), 119.8 (CH), 115.5 (CH), 83.6 (C), 39.7 (CH_2), 33.4 (CH), 28.4 (CH_3), 20.0 (CH_3); Found (FTMS + p NSI) $[M + NH_4]^+$ 448.2227, $C_{26}H_{30}N_3O_4$ requires 448.2231; $[\alpha]_D^{22\,°C}$ = -1.5 (c = 1.34 in EtOH); CSP-HPLC (Chiralpak IB, 99.5:0.5 hexane:IPA, 1 ml min^{-1}) (*R*)-**3.3ef** 18.5 min and (*S*)-**3.3ef** 23.1 min.

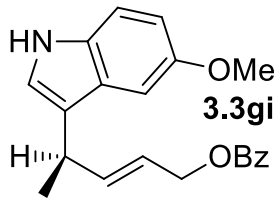
(*R,E*)-2-(4-(5-Chloro-1H-indol-3-yl)pent-2-en-1-yl)isoindoline-1,3-dione (3.3eg)



General procedure followed and crude purified by column chromatography (eluent: 5:1 to 3:1 petrol 40-60 °C/EtOAc) to yield product **3.3eg** as a light yellow oil (52.6 mg, 0.14 mmol, 96%, 15:1 regioselectivity, 85:15 e.r.).

R_F 0.30 (3:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 3399 (br, N-H), 3018, 2966, 2930 (C-H), 1705 (C=O), 1615, 1464 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (1H, br s, NH), 7.87-7.78 (2H, m, Phth), 7.74-7.65 (2H, m, Phth), 7.52 (1H, d, *J* = 1.9 Hz, indole), 7.22 (1H, d, *J* = 8.6 Hz, indole), 7.07 (1H, dd, *J* = 8.6, 2.0 Hz, indole), 6.94 (1H, d, *J* = 2.2 Hz, NC<u>H</u>=C), 6.00 (1H, ddt, *J* = 15.4, 6.6, 1.3 Hz, =C<u>H</u>CH), 5.60 (1H, dtd, *J* = 15.4, 6.3, 1.4 Hz, =C<u>H</u>CH$_2$), 4.29 (2H, d, *J* = 6.3 Hz, CH_2), 3.66 (1H, app. p, *J* = 6.8 Hz, C<u>H</u>CH$_3$), 1.40 (2H, d, *J* = 7.0 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2 (C), 139.2 (CH), 135.0 (C), 134.0 (CH), 132.3 (C), 127.8 (C), 124.9 (C), 123.4 (CH), 122.2 (CH), 122.1 (CH), 119.9 (C), 119.0 (CH), 112.2 (CH), 39.7 (CH_2), 33.4 (CH), 20.5 (CH_3); Found (FTMS + p NSI) $[M + H]^+$ 365.1054, $C_{21}H_{18}ClN_2O_2$ requires 365.1051; $[\alpha]_D^{21\,°C}$ = +15.3 (c = 3.65 in $CHCl_3$); CSP-HPLC (Chiralpak IB, 90:10 hexane:IPA, 1 ml min^{-1}) (*R*)-**3.3eg** 19.0 min and (*S*)-**3.3eg** 20.3 min.

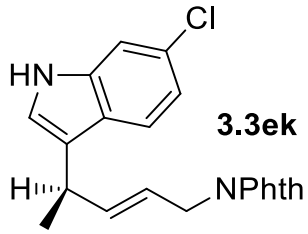
(*R,E*)-4-(5-Methoxy-1H-indol-3-yl)pent-2-en-1-yl benzoate (3.3gi)



General procedure followed and crude purified by column chromatography (eluent: 12:1 to 6:1 petrol 40-60 °C/EtOAc) to yield product **3.3gi** as a light yellow oil (33.7 mg, 0.10 mmol, 67%, 11:1 regioselectivity, 97:3 e.r.).

R_F 0.23 (6:1 hexane/Et_2O); ν_{max}/cm^{-1} 3401 (br, N-H), 3008, 2961, 2932 (C-H), 1708 (C=O), 1483 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01-7.91 (2H, m, Ar-H), 7.92 (1H, br s, NH), 7.52-7.40 (1H, m, Ar-H), 7.39-7.28 (2H, m, Ar-H), 7.20-7.09 (2H, m, indole), 6.98 (1H, d, *J* = 2.4 Hz, indole), 6.86 (1H, d, *J* = 2.3 Hz, indole), 6.76 (1H, dd, *J* = 8.8, 2.4 Hz, indole), 6.01 (1H, dd, *J* = 15.4, 6.7 Hz, =C<u>H</u>CH), 5.72 (1H, dtd, *J* = 15.4, 6.3, 1.3 Hz, C<u>H</u>CH$_2$), 4.73 (2H, d, *J* = 6.3 Hz, CH_2O), 3.72 (3H, s, OCH_3), 3.67 (1H, m, C<u>H</u>CH$_3$), 1.40 (3H, d, *J* = 7.0 Hz, CHC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6 (C), 153.9 (C), 140.6 (CH), 133.0 (CH), 131.9 (C), 130.5 (C), 129.7 (CH), 128.4 (CH), 127.2 (C), 122.5 (CH), 121.5 (CH), 119.6 (C), 112.2 (CH), 112.0 (CH), 101.6 (CH), 65.8 (CH_2), 56.0 (CH_3), 33.8 (CH), 20.3 (CH_3); Found (FTMS + p NSI) $[M + H]^+$ 336.1598, $C_{21}H_{22}NO_3$ requires 336.1594; $[\alpha]_D^{24\,°C}$ = -1.6 (c = 2.43 in $CHCl_3$); CSP-HPLC (Chiralcel OD-H, 20:1 hexane:IPA, 1 ml min^{-1}) (*R*)-**3.3gi** 64.3 min and (*S*)-**3.3gi** 69.7 min.

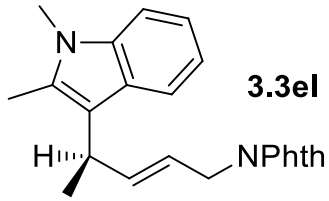
(*R,E*)-2-(4-(6-Chloro-1H-indol-3-yl)pent-2-en-1-yl)isoindoline-1,3-dione (3.3ek)



General procedure followed and crude purified by column chromatography (eluent: 5:1 to 4:1 petrol 40-60 °C/EtOAc) to yield product **3.3ek** as a light yellow oil (53.8 mg, 0.15 mmol, 98%, 15:1 regioselectivity, 82:18 e.r.).

R_F 0.29 (3:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 3370 (br, N-H), 2967, 2930 (C-H), 1704 (C=O), 1615, 1455 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (1H, br s, NH), 7.88-7.78 (2H, m, Phth), 7.74-7.65 (2H, m, Phth), 7.45 (1H, d, *J* = 8.4 Hz, indole), 7.29 (1H, d, *J* = 1.3 Hz, indole), 6.98 (1H, dd, *J* = 8.4, 1.8 Hz, indole), 6.91 (1H, d, *J* = 2.2 Hz, indole), 5.99 (1H, ddt, *J* = 15.4, 6.6, 1.2 Hz, =C<u>H</u>CH), 5.60 (1H, dtd, *J* = 15.4, 6.2, 1.2 Hz, =C<u>H</u>CH_2), 4.29 (2H, d, *J* = 6.2 Hz, CH_2), 3.69 (1H, m, C<u>H</u>CH_3), 1.40 (3H, d, *J* = 7.2 Hz, CHC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3 (C), 139.2 (CH), 137.0 (C), 134.1 (CH), 132.3 (C), 127.9 (C), 125.4 (C), 123.4 (CH), 122.2 (CH), 121.4 (CH), 120.5 (CH), 120.4 (C), 120.0 (CH), 111.2 (CH), 39.7 (CH_2), 33.5 (CH), 20.5 (CH_3); Found (FTMS + p NSI) $[M + H]^+$ 365.1056, $C_{21}H_{18}ClN_2O_2$ requires 365.1051; $[\alpha]_D^{23\ °C}$ = -1.0 (c = 2.06 in $CHCl_3$); CSP-HPLC (Chiralpak IB, 10:1 hexane:IPA, 1 ml min^{-1}) (*R*)-**3.3ek** 17.1 min and (*S*)-**3.3ek** 18.8 min.

(*R,E*)-2-(4-(1,2-Dimethyl-1H-indol-3-yl)pent-2-en-1-yl)isoindoline-1,3-dione (3.3el)

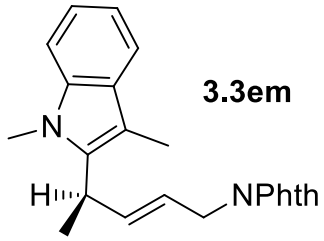


General procedure followed and crude purified by column chromatography (eluent: 8:1 to 5:1 petrol 40-60 °C/EtOAc) to yield product **3.3el** as a light yellow oil (49.7 mg, 0.14 mmol, 92%, >20:1 regioselectivity, 98:2 e.r.).

R_F 0.30 (5:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 3019, 2976, 2927 (C-H), 1708 (C=O), 1614, 1468 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91-7.78 (2H, m, Phth), 7.76-7.63

(2H, m, Phth), 7.56 (1H, d, *J* = 8.0 Hz, indole), 7.24 (1H, d, *J* = 8.1 Hz, indole), 7.13 (1H, app. t, *J* = 7.5 Hz, indole), 7.00 (1H, app. t, *J* = 7.9 Hz, indole), 6.15 (1H, dd, *J* = 15.4, 5.1 Hz, =C<u>H</u>CH), 5.62 (1H, dt, *J* = 15.4, 6.2 Hz, C<u>H</u>CH_2), 4.31 (2H, d, *J* = 6.2 Hz, CH_2N), 3.71-3.86 (1H, m, C<u>H</u>CH_3), 3.63 (3H, s, NCH_3), 2.34 (3H, s, CH_3), 1.47 (3H, d, *J* = 7.2 Hz, CHC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1 (C), 139.4 (CH), 136.7 (C), 133.9 (CH), 132.32 (C), 132.28 (C), 126.5 (C), 123.3 (CH), 121.5 (CH), 120.4 (CH), 119.2 (CH), 118.6 (CH), 113.8 (C), 108.7 (CH), 39.7 (CH_2), 33.2 (CH), 29.5 (CH_3), 20.2 (CH_3), 10.6 (CH_3); Found (FTMS + p NSI) $[M + H]^+$ 359.1757, $C_{23}H_{23}N_2O_2$ requires 359.1754; $[\alpha]_D^{24\,°C}$ = -16.4 (c = 2.93 in $CHCl_3$); CSP-HPLC (Chiralpak IC, 95:5 hexane:IPA, 1 ml min^{-1}) (*R*)-**3.3el** 21.2 min and (*S*)-**3.3el** 25.6 min.

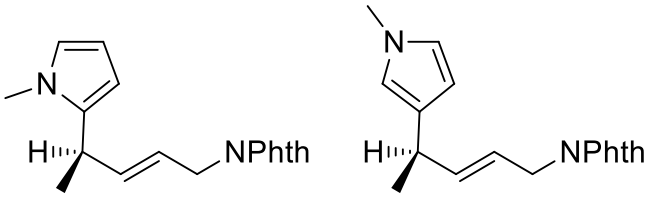
(*R,E*)-2-(4-(1,3-Dimethyl-1H-indol-2-yl)pent-2-en-1-yl)isoindoline-1,3-dione (3.3em)



General procedure followed and crude purified by column chromatography (eluent: 8:1 to 6:1 petrol 40-60 °C/EtOAc) to yield product **3.3em** as a light yellow oil (25.5 mg, 0.07 mmol, 48%, >20:1 regioselectivity , 82:18 e.r.).

R_F 0.17 (8:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2969, 2929 (C-H), 1709 (C=O), 1613, 1469 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89-7.81 (2H, m, Phth), 7.76-7.67 (2H, m, Phth), 7.49 (1H, d, *J* = 7.7 Hz, indole), 7.22 (1H, d, *J* = 8.0 Hz, indole), 7.15 (1H, ddd, *J* = 8.0, 6.9, 1.2 Hz, indole), 7.06 (1H, ddd, *J* = 7.7, 6.9, 1.3 Hz, indole), 6.00 (1H, ddt, *J* = 15.6, 4.4, 1.5 Hz, =C<u>H</u>CH), 5.56 (1H, dtd, *J* = 15.6, 5.9, 2.2 Hz, =C<u>H</u>CH_2), 4.32 (2H, app. dt, *J* = 5.9, 1.5 Hz, CHC<u>H</u>$_2$), 3.90-3.86 (1H, m, C<u>H</u>CH_3), 3.63 (3H, s, NCH_3), 2.25 (3H, s, CH_3), 1.46 (3H, d, *J* = 7.3 Hz, CHC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1 (C), 138.0 (C), 136.8 (C), 136.5 (CH), 134.1 (CH), 132.3 (C), 128.5 (C), 123.4 (CH), 123.2 (CH), 121.0 (CH), 118.8 (CH), 118.3 (CH), 108.7 (CH), 106.7 (C), 39.5 (CH_2), 32.7 (CH), 30.6 (CH_3), 18.7 (CH_3), 9.2 (CH_3); Found (FTMS + p NSI) $[M + H]^+$ 359.1756, $C_{23}H_{23}N_2O_2$ requires 359.1754; $[\alpha]_D^{22\,°C}$ = -3.5 (c = 1.72 in $CHCl_3$); CSP-HPLC (Chiralpak IA, 96:4 hexane:IPA, 1 ml min^{-1}) (*R*)-**3.3em** 13.2 min and (*S*)-**3.3em** 14.1 min.

(*R,E*)-2-(4-(1-Methyl-1H-pyrrol-2-yl)pent-2-en-1-yl)isoindoline-1,3-dione (3.3en) + (*R,E*)-2-(4-(1-Methyl-1H-pyrrol-3-yl)pent-2-en-1-yl)isoindoline-1,3-dione (3.3en'')



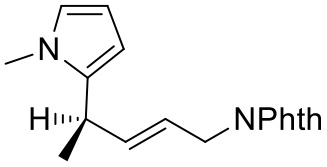
3.3en **3.3en''**

General procedure followed and crude purified by column chromatography (eluent: 6:1 petrol 40-60 °C/EtOAc) to yield a 1:1 mixture of isomers **3.3en** and **3.3en''** as a brown oil (25.4 mg, 0.09 mmol, 58%, >20:1 regioselectivity).

R_F 0.58 (5:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2966, 2930 (C-H), 1708 (C=O), 1613, 1429 (C-C Ar); Found (FTMS + p NSI) $[M + H]^+$ 295.1443, $C_{18}H_{19}N_2O_2$ requires 295.1441;

Partial separation of the two isomers was achieved by 5% $AgNO_3$/silica column chromatography (eluent: 3:1 to 1:3 petrol 40-60 °C/EtOAc) for characterisation purposes.

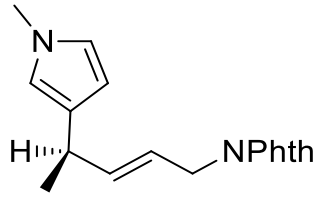
(*R,E*)-2-(4-(1-Methyl-1H-pyrrol-2-yl)pent-2-en-1-yl)isoindoline-1,3-dione (3.3en)



3.3en

Using 1 M $AgNO_3$ in MeCN dipped TLC plates R_F 0.20 (1:1 petrol 40-60 °C/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92-7.78 (2H, m, Phth), 7.78-7.66 (2H, m, Phth), 6.52 (1H, app. t, *J* = 2.3 Hz, pyrrole), 6.05 (1H, app. t, *J* = 3.3 Hz, pyrrole), 5.90 (1H, dd, *J* = 3.6, 1.9, Hz, pyrrole), 5.79 (1H, ddt, *J* = 15.4, 6.9, 1.4 Hz, =C<u>H</u>CH), 5.42 (1H, dtd, *J* = 15.4, 5.9, 1.2 Hz, =C<u>H</u>CH_2), 4.25 (2H, d, *J* = 5.9 Hz, NCH_2), 3.48 (3H, s, NCH_3), 3.50-3.36 (1H, m, C<u>H</u>CH_3), 1.34 (3H, d, *J* = 7.0 Hz, CHC<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1 (C), 138.3 (CH), 135.6 (C), 134.1 (CH), 132.4 (C), 123.4 (CH), 122.7 (CH), 121.9 (CH), 106.6 (CH), 105.0 (CH), 39.5 (CH_2), 34.2 (CH), 33.9 (CH_3), 20.0 (CH_3).

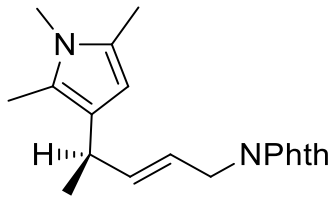
(*R,E*)-2-(4-(1-Methyl-1H-pyrrol-3-yl)pent-2-en-1-yl)isoindoline-1,3-dione (3.3en'')



3.3en''

Using 1 M $AgNO_3$ in MeCN dipped TLC plates R_F 0.26 (1:1 petrol 40-60 °C/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90-7.78 (2H, m, Phth), 7.77-7.66 (2H, m, Phth), 6.50 (1H, app. t, *J* = 2.4 Hz, pyrrole), 6.36 (1H, app. t, *J* = 1.7 Hz, pyrrole), 5.96 (1H, app. t, *J* = 2.1 Hz, pyrrole), 5.87 (1H, ddt, *J* = 15.3, 7.2, 1.3 Hz, =C<u>H</u>CH), 5.53 (1H, dtd, *J* = 15.3, 6.6, 1.2 Hz, =C<u>H</u>CH_2), 4.27 (2H, d, *J* = 6.6 Hz, NCH_2), 3.59 (3H, s, NCH_3), 3.35 (1H, app. p, *J* = 7.0 Hz, C<u>H</u>CH_3), 1.26 (3H, d, *J* = 7.0 Hz, CHC<u>H</u>$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1 (C), 140.5 (CH), 134.0 (C), 132.5 (C), 128.4 (CH), 123.4 (CH), 121.8 (CH), 121.2 (CH), 118.6 (CH), 107.3 (CH), 39.8 (CH_3), 36.2 (CH_2), 34.8 (CH), 21.4 (CH_3).

(*R,E*)-2-(4-(1,2,5-Trimethyl-1H-pyrrol-3-yl)pent-2-en-1-yl)isoindoline-1,3-dione (3.3eo)



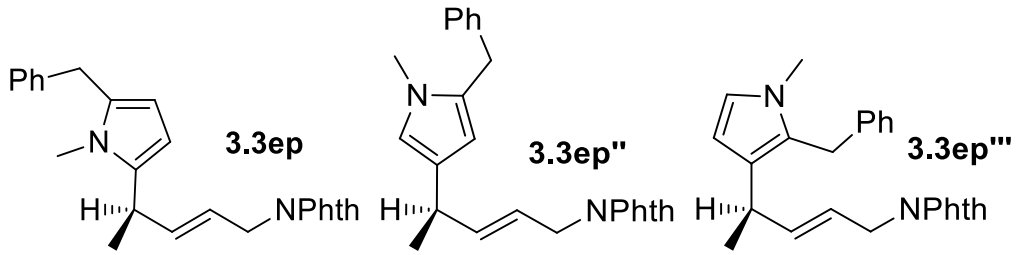
3.3eo

General procedure followed using 15 mol% catalyst and crude purified by column chromatography (eluent: 15:1 to 8:1 petrol 40-60 °C/EtOAc) to yield product **3.3eo** as a brown oil (23.3% mg, 0.07 mmol, 48%, >20:1 regioselectivity, 98:2 e.r.).

R_F 0.40 (5:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2927 (C-H), 1707 (C=O), 1651, 1466 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89-7.78 (2H, m, Phth), 7.78-7.63 (2H, m, Phth), 5.87 (1H, dd, *J* = 15.3, 6.7 Hz, =C<u>H</u>CH), 5.67 (1H, s, pyrrole), 5.49 (1H, dtd, *J* = 15.3, 6.3, 1.3 Hz, =C<u>H</u>CH_2), 4.24 (2H, d, *J* = 6.3 Hz, =CHC<u>H</u>$_2$), 3.24-3.41 (1H, m, C<u>H</u>CH_3), 3.33 (3H, s, NCH_3), 2.17 (3H, s, CH_3), 2.09 (3H, s, CH_3), 1.24 (3H, d, *J* = 7.1 Hz, CHC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2 (C), 140.8 (CH), 133.9 (CH), 132.4 (C), 126.9 (C), 123.32 (CH), 123.30 (C), 121.6 (C), 120.4 (CH), 103.5 (CH), 39.9 (CH_2), 33.8 (CH), 30.2 (CH_3), 21.4 (CH_3), 12.6 (CH_3), 10.3 (CH_3); Found (FTMS + p NSI) $[M + H]^+$ 323.1757, $C_{20}H_{23}N_2O_2$

requires 323.1754; $[\alpha]_D^{22\,°C}$ = -6.9 (c = 0.58 in $CHCl_3$); CSP-HPLC (Chiralpak IC, 95:5 hexane:IPA, 1 ml min^{-1}) (*R*)-**3.3eo** 14.4 min and (*S*)-**3.3eo** 16.7 min.

(*R,E*)-2-(4-(5-Benzyl-1-methyl-1H-pyrrol-2-yl)pent-2-en-1-yl)isoindoline-1,3-dione (3.3ep) + (*R,E*)-2-(4-(5-benzyl-1-methyl-1H-pyrrol-3-yl)pent-2-en-1-yl)isoindoline-1,3-dione (3.3ep'') + (*R,E*)-2-(4-(2-benzyl-1-methyl-1H-pyrrol-3-yl)pent-2-en-1-yl)isoindoline-1,3-dione (3.3ep''')

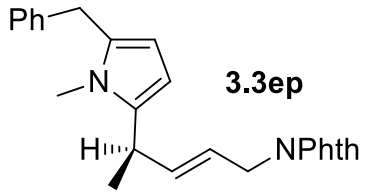


General procedure followed and crude purified by column chromatography (eluent: 10:1 to 4:1 petrol 40-60 °C/EtOAc) to yield a 5:1:1 mixture of isomers **3.3ep, 3.3ep''** and **3.3ep'''** as a brown oil (34.9 mg, 0.09 mmol, 60%) and a complex mixture of **3.3ep'** isomers (7.5 mg, 0.02 mmol, 13%, giving 5:1 regioselectivity).

R_F was not measured as the products streaked badly.

Partial separation of the major isomer from the two other isomers was achieved by 5% $AgNO_3$/silica column chromatography (eluent: 3:1 to 2:1 petrol 40-60 °C/EtOAc) for characterisation purposes.

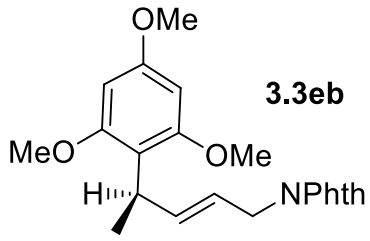
(*R,E*)-2-(4-(5-Benzyl-1-methyl-1H-pyrrol-2-yl)pent-2-en-1-yl)isoindoline-1,3-dione (3.3ep)



Using 1 M $AgNO_3$ in MeCN dipped TLC plates R_F 0.22 (2:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2973, 2929, 2868 (C-H), 1712 (C=O), 1494 (C-C Ar); ^1H NMR (300 MHz, $CDCl_3$) δ 7.87-7.80 (2H, m, Phth), 7.76-7.68 (2H, m, Phth), 7.25-7.07 (5H, m, Ar-H), 5.85 (1H, d, *J* = 3.4 Hz, pyrrole), 5.79 (1H, app. dt, *J* = 15.4, 1.3 Hz, =C<u>H</u>CH), 5.78 (1H, d, *J* = 3.4 Hz, pyrrole), 5.39 (1H, dtd, *J* = 15.4, 6.1, 1.2 Hz, =C<u>H</u>CH_2), 4.24 (2H, d, *J* = 6.1 Hz, CH_2N), 3.90 (2H, s, CH_2Ph), 3.41 (1H, app. p, *J* = 7.4 Hz, C<u>H</u>CH_3), 3.23 (3H, s, NCH_3), 1.33 (3H, d,

J = 7.0 Hz, CHC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5 (C), 140.0 (C), 138.8 (CH), 136.0 (C), 134.5 (CH), 132.7 (C), 131.8 (C), 129.0 (CH), 128.9 (CH), 126.6 (CH), 123.8 (CH), 123.0 (CH), 106.9 (CH), 103.9 (CH), 39.9 (CH_2), 34.9 (CH), 33.8 (CH_2), 31.1 (CH_3), 20.3 (CH_3); Found (FTMS + p NSI) $[M + H]^+$ 395.1909, $C_{25}H_{25}N_2O_2$ requires 395.1911.

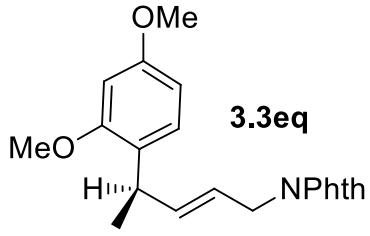
(*R,E*)-2-(4-(2,4,6-Trimethoxyphenyl)pent-2-en-1-yl)isoindoline-1,3-dione (3.3eb)



General procedure followed and crude purified by column chromatography (eluent: 4:1 petrol 40-60 °C/EtOAc) to yield product **3.3eb** as a white crystalline solid (56.0 mg, 0.15 mmol, 98%, >20:1 regioselectivity, 90:10 e.r.).

R_F 0.25 (4:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2937, 2871, 2838 (C-H), 1705 (C=O), 1606, 1588, 1464 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88-7.76 (2H, m, Phth), 7.75-7.62 (2H, m, Phth), 6.15 (1H, ddt, *J* = 15.4, 6.9, 1.2 Hz, =C<u>H</u>CH_2), 6.09 (2H, s, Ar-H), 5.49 (1H, dtd, *J* = 15.4, 6.4, 1.4 Hz, =C<u>H</u>CH_2), 4.22 (2H, d, *J* = 6.4 Hz, CH_2N), 4.02 (1H, app. p, *J* = 7.1 Hz, C<u>H</u>CH_3), 3.77 (3H, s, OCH_3), 3.73 (6H, s, $2OCH_3$), 1.27 (3H, d, *J* = 7.1 Hz, CHC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1 (C), 159.4 (C), 158.8 (C), 139.9 (CH), 133.9 (CH), 132.4 (C), 123.2 (CH), 120.7 (CH), 114.4 (C), 91.3 (CH), 55.8 (CH_3), 55.3 (CH_3), 39.9 (CH_2), 31.7 (CH), 19.0 (CH_3); Found (FTMS + p NSI) $[M + H]^+$ 382.1648, $C_{22}H_{24}NO_5$ requires 382.1649; $[\alpha]_D^{17\,°C}$ = +2.9 (c = 3.44 in $CHCl_3$); CSP-HPLC (Chiralpak IA, 95.5 hexane:IPA, 1 ml min^{-1}) (*R*)-**3.3eb** 13.1 min and (*S*)-**3.3eb** 15.2 min; m.p. 127 °C (Et_2O/hexane).

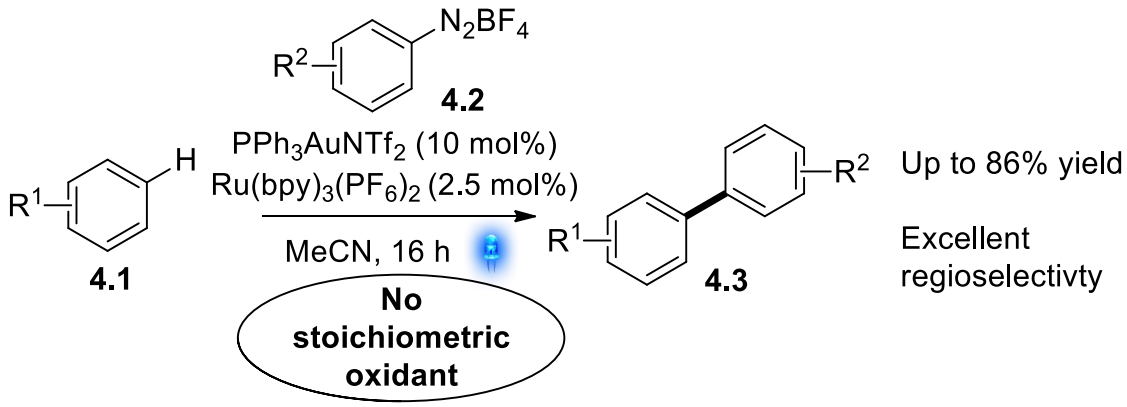
(*R,E*)-2-(4-(2,4-Dimethoxyphenyl)pent-2-en-1-yl)isoindoline-1,3-dione (3.3eq)



General procedure followed and crude purified by column chromatography (eluent: 8:1 to 6:1 petrol 40-60 ^{o}C/EtOAc) to yield product **3.3eq** as a white oily paste (51.1 mg, 0.15 mmol, 97%, 10:1 regioselectivity, 57:43 e.r.).

R_F 0.30 (6:1 petrol 40-60 ^{o}C/EtOAc); ν_{max}/cm^{-1} 3012, 2961, 2934, 2836 (C-H), 1709 (C=O), 1610, 1586, 1504, 1466 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89-7.79 (2H, m, Phth), 7.76-7.64 (2H, m, Phth), 7.00 (1H, d, *J* = 9.0 Hz, Ar-H), 6.48-6.39 (2H, m, Ar-H), 5.94 (1H, ddt, *J* = 15.4, 5.7, 1.0 Hz, =C<u>H</u>CH), 5.52 (1H, dtd, *J* = 15.4, 6.2, 1.6 Hz, =C<u>H</u>CH_2), 4.27 (2H, d, *J* = 6.2 Hz, CH_2N), 3.79 (1H, m, C<u>H</u>CH_3), 3.78 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 1.24 (3H, d, *J* = 7.0 Hz, CHC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1 (C), 159.2 (C), 157.7 (C), 139.3 (CH), 132.0 (CH), 132.4 (C), 127.9 (CH), 126.3 (C), 123.3 (CH), 121.6 (CH), 104.2 (CH), 98.7 (CH), 55.5 (CH_3), 55.4 (CH_3), 39.9 (CH_2), 34.1 (CH), 19.9 (CH_3); Found (FTMS + p NSI) $[M + H]^+$ 352.1546, $C_{21}H_{22}NO_4$ requires 352.1543; CSP-HPLC (Chiralpak IB, 99:1 hexane:IPA, 1 ml min^{-1}) (*R*)-**3.3eq** 21.3 min and (*S*)-**3.3eq** 25.6 min.

Chapter 4: Dual gold- and photoredox-catalysed C–H activation



Acknowledgments

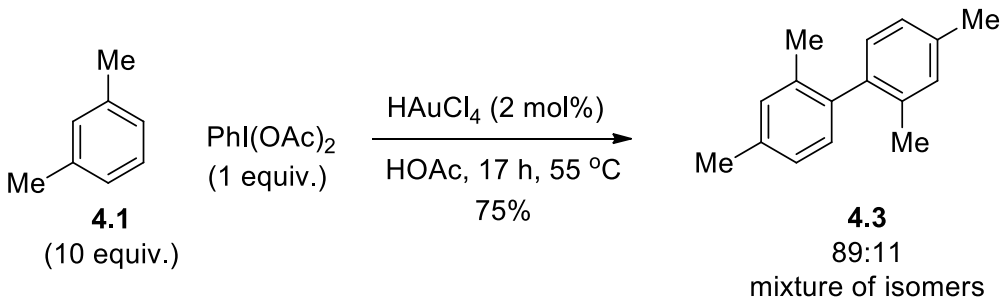
The author would like to thank Vincent Gauchot for his collaboration on this project. All work completed by Vincent is clearly marked with Я.

4.1 Introduction

4.1.1 Previous developments in gold C-H activation

The design of greener methods for synthesis has become an important and heavily researched area of chemistry.[91] This drive towards greener methods has led to increased investigation into C-H functionalisation reactions which can greatly improve atom economy by removing the requirement for prefunctionalisation of substrates. Much of the research in this area focuses on the use of palladium, ruthenium and rhodium as the transition metal catalysts for C-H activation.[92-98] However, gold has also been shown to activate C-H bonds under mild conditions. In addition to the attractive mild conditions under which gold can achieve C-H activation, gold also reacts regioselectively, removing the need for chelate-assisted directing groups and thus further increasing atom efficiency.[99-101] These remarkable properties of gold allow for regioselective aryl-aryl cross-coupling reactions; a much sought after method for the preparation of highly valuable biaryl motifs.[102]

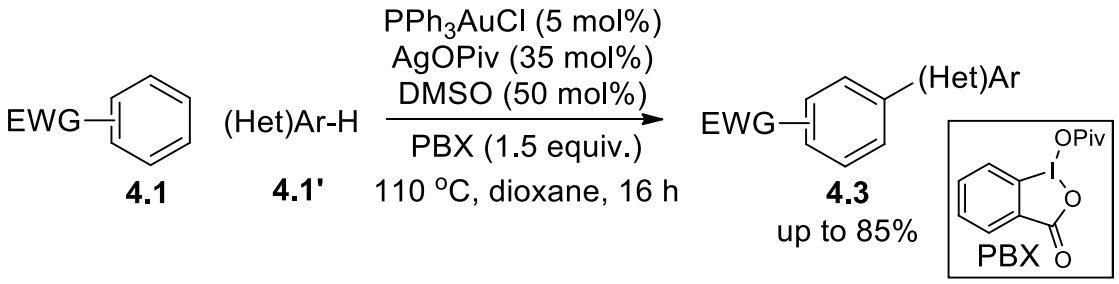
Gold-catalysed C-H activation for aryl coupling was first demonstrated in a double C-H activation homocoupling methodology reported by Tse and co-workers (Scheme 4.1).[103, 104]



Scheme 4.1: Example of aryl homocoupling through double gold C-H activation[103, 104]

The mechanism of this reaction is not discussed in detail but the results clearly demonstrate that it is possible for gold to catalyse aryl-aryl couplings and shows the potential for these couplings to be regioselective. Cross-coupling reactions were also attempted by Tse's group but the selectivity observed was very low.[104] Another drawback to this seminal work is the use of the oxidant rather than the arene as the limiting reagent.

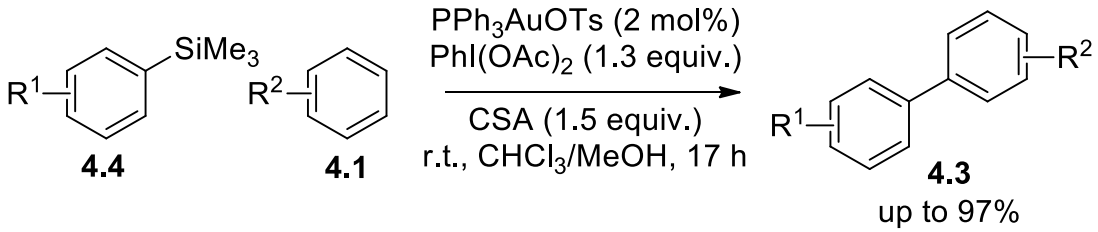
Double C-H activation cross-couplings were later achieved by Larrosa under much improved conditions (Scheme 4.2).[105] The gold-catalysed conditions allowed for the selective coupling of very electron-poor arenes with electron-rich heterocycles or arenes.



Scheme 4.2: Cross-coupling through double gold C-H activation[105]

Larrosa proposes that both coupling partners undergo C-H functionalization by gold catalysis with the selectivity being determined by the difference in preferred reactivity of gold(I) and gold(III). Gold(I) is thought to undergo C-H activation through a concerted metalation–deprotonation step and so selectively activates the most acidic C-H bond available. Conversely, gold(III) has been shown to readily undergo electrophilic aromatic substitution and so reacts preferentially with electron-rich aryls.[106] This difference in reactivity allowed for the design of a catalytic cycle whereby the gold(I) reacts first with the electron-poor arene which has the most acidic protons and then, after oxidation, the gold(III) will selectively react with the more electron-rich coupling partner to give selective cross-couplings.

The selectivity observed in Larrosa's methodology is dependent on the coupling partners being very electron-poor and very electron-rich respectively, which limits the scope of the reaction. The temperature required for the reaction is also quite high, likely due to the difficult gold(I) C-H activation step required for the mechanism. In order to broaden the scope of gold-catalysed C-H functionalisations and also avoid the difficult gold(I) C-H activation step, other groups have used functionalised arenes as one of the coupling partners. This was pioneered by Lloyd-Jones and Russell who reported the first successful gold-catalysed cross-coupling of arylsilanes and arenes (Scheme 4.3).[102, 107]



Scheme 4.3: Seminal work on site selective arylation of arylsilanes[102, 107]

Lloyd-Jones and Russell elegantly demonstrate the selectivity of the gold catalysts to preferentially activate one C-H bond, achieving excellent regioselectivity in a range of products. They also demonstrated that gold, unlike other transition metals, is tolerant of a range of functional groups, including bromo-groups which are unsuited to palladium cross-couplings.[102, 107] A detailed investigation of the mechanism of this reaction shows that the gold(I) catalyst is first oxidised to gold(III) and then adds into the more reactive Si-C bond in a chemoselective manner. After ligand exchange, the gold catalyst, at this point in the cycle, much prefers to coordinate with the more electron-rich coupling partner and so the C-H activation step occurs exclusively with the arene, giving excellent selectivity for heterocoupling. The selectivity for heterocoupling is therefore dependent on the arene being more electron-rich than the arylsilane, limiting slightly, the otherwise broad scope of this reaction.

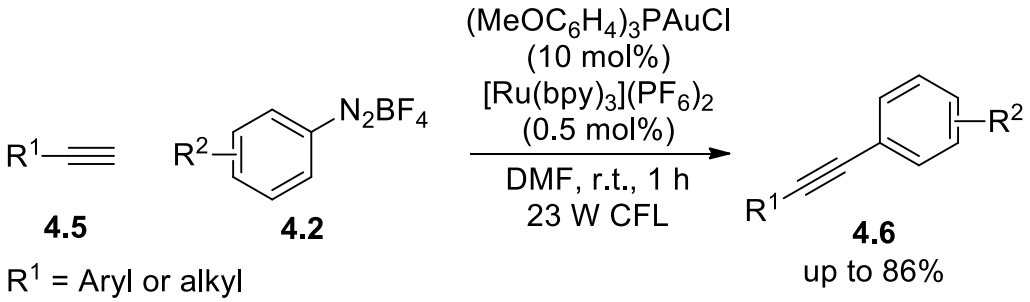
Despite these impressive advances in gold-catalysed aryl-aryl couplings through C-H activation, there are still two main limitations in this field, the first being the restricted arene scope. Under mild conditions, gold(III) C-H bond activation is only observed with electron-rich or electron neutral arenes and so the arene scope for gold-catalysed C-H activations does not extend to electron-poor arenes. The second limitation of the previous work in this area is the requirement for stoichiometric amounts of oxidant.[14] Stoichiometric oxidant is essential in these procedures in order to access the Au(I)/Au(III) cycle necessary for cross-couplings. Additionally, the oxidant must also be relatively strong due to the high redox potential of the Au(I)/Au(III) couple (E_0 = 1.41 V).[108] However, it would be much more beneficial to employ a catalytic and mild oxidant in place of the stoichiometric oxidant, which would avoid the generation of stoichiometric amounts of waste from the stoichiometric oxidant. This is particularly pertinent in C-H activation reactions as some of the benefits of not requiring

prefunctionalisation are lost by the generation of stoichiometric waste. Additionally, the use of stoichiometric oxidant limits the scope of the reaction to oxidant tolerant substrates. Employing photoredox catalysis to access the Au(I)/Au(III) cycle required for cross-couplings offers an attractive alternative to stoichiometric oxidants and has recently been investigated in gold-catalysed couplings. Importantly however, prior to this project, gold catalysed C(sp^2)-H activation through photoredox catalysis had not been achieved.

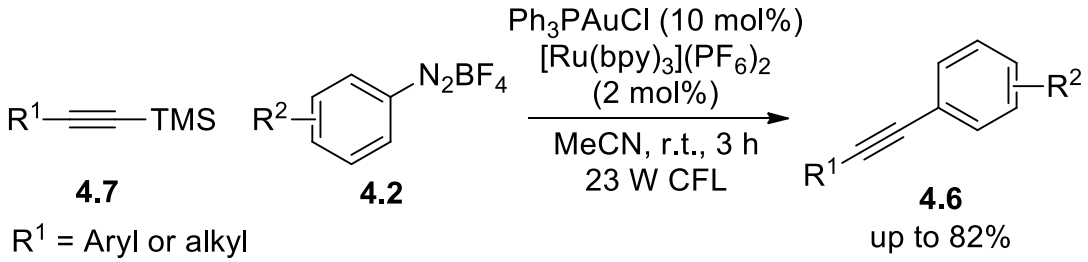
4.1.2 Previous developments in dual gold- and photoredox-catalysis

The use of visible light over conventional energy sources to drive organic transformations has been heavily investigated in recent years.[109] This surge in research activity is partly due to the numerous environmental and economic benefits visible light driven reactions have over more conventional methods. Furthermore, the use of a photocatalyst, especially in cooperation with transition metal catalysis, has led to a wealth of entirely new transformations using visible light. The dual photoredox and transition metal catalysed coupling of aryl diazonium salts has been particularly useful in the development of new coupling reactions.[110, 111] Accessing the Au(I)/Au(III) redox cycle of gold catalysts in this way is of particular interest as, due to gold(I)'s reluctance to oxidise, photoredox catalysis provides a mild alternative to using harsh stoichiometric oxidants.

Dual gold- and photoredox- catalysis was first utilised to expand on established gold-catalysed transformations by replacing the typical protodeauration step with reductive elimination to give a new C-C bonds. This work was initially developed by Glorius (2013)[112] and Toste (2014)[113] and has been recently reviewed.[109, 114, 115] Also, photoredox-catalysed couplings can be performed without a separate photocatalyst using a digold catalyst.[115] For the purposes of this introduction however, the focus will be on dual gold and photoredox-catalysed cross-couplings[114] which are more relevant to this work.

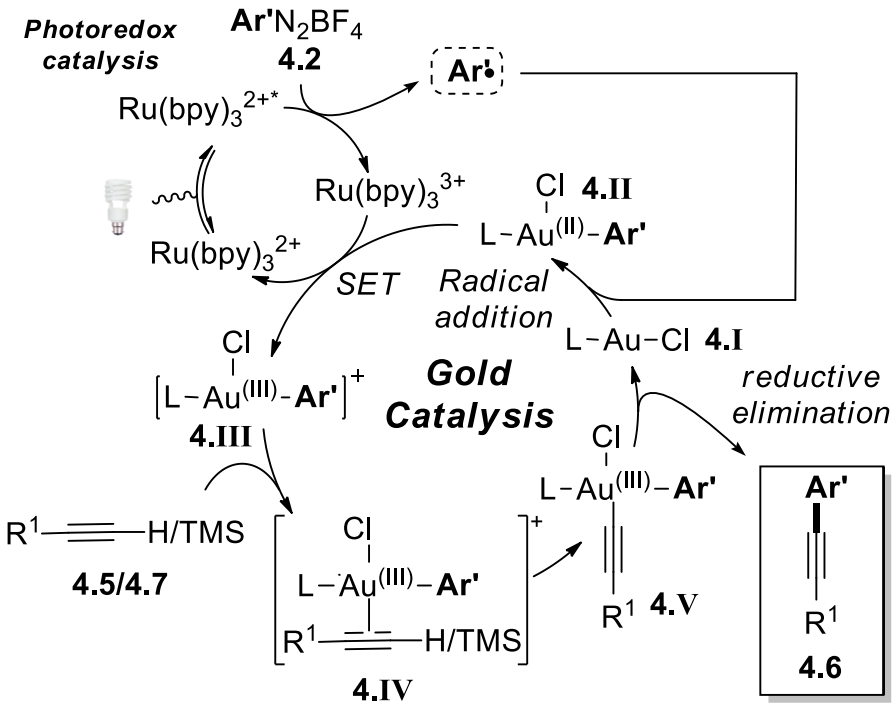


Scheme 4.4: Dual gold and photoredox-catalysed arylation of terminal alkynes reported by Glorius and co-workers[116]

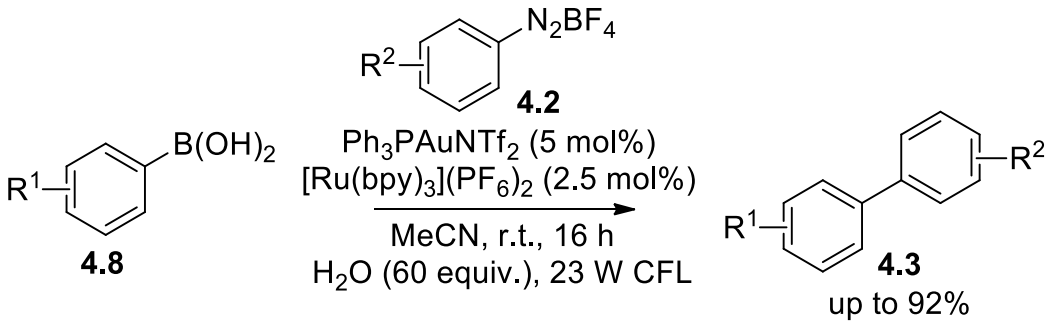


Scheme 4.5: Dual gold and photoredox-catalysed arylation of alkynyltrimethylsilanes reported by Toste and co-workers[117]

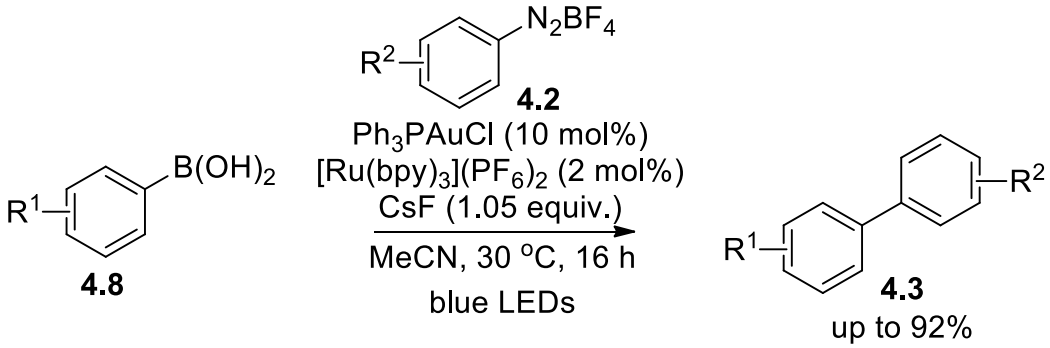
The first C-C bond forming reaction to utilise dual gold- and photoredox- catalysis was carried out independently by both Glorius (Scheme 4.4)[116] and Toste (Scheme 4.5)[117] in 2016. The Sonogashira-type couplings proceed through the same general mechanism shown below (Scheme 4.6). Excitation of the ruthenium photocatalyst allows for the generation of an aryl radical from the diazonium salt which then adds to the gold(I) catalyst **4.I** to give intermediate **4.II**. The gold(II) complex **4.II** is then oxidised to gold(III) **4.III** through SET to regenerate the ground state ruthenium catalyst. The gold(III) catalyst then coordinates to the alkyne (intermediate **4.IV**), undergoes C-H or C-Si insertion (intermediate **4.V**) and then reductive elimination to provide the substituted alkyne product **4.6**.



Scheme 4.6: Proposed mechanism of the dual gold and photoredox-catalysed Sonogashira-type couplings[116, 117]

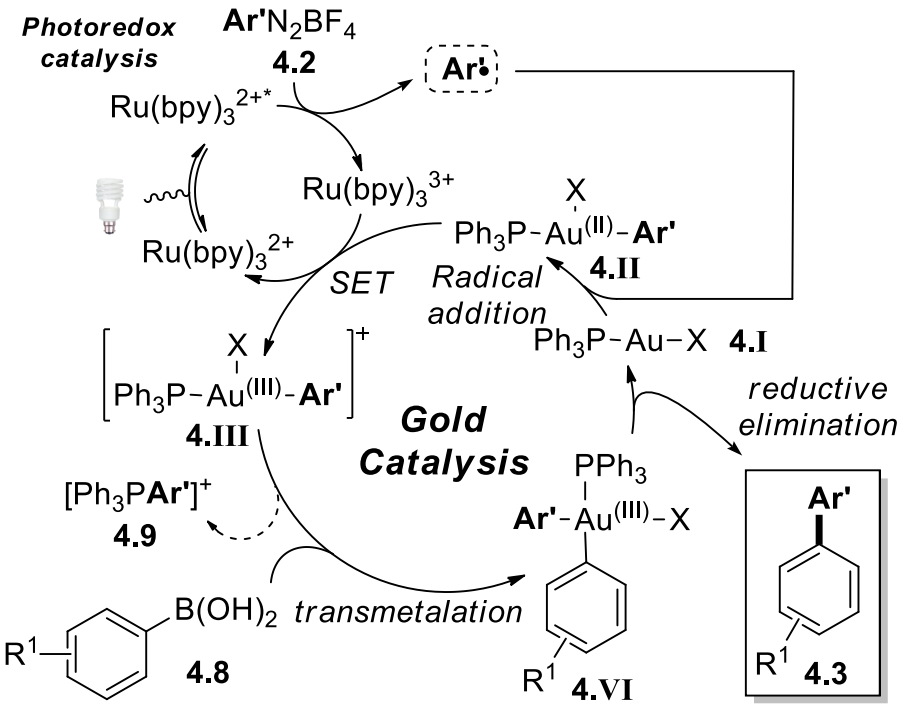


Scheme 4.7: Suzuki-type coupling reported previously in the Lee group[118]

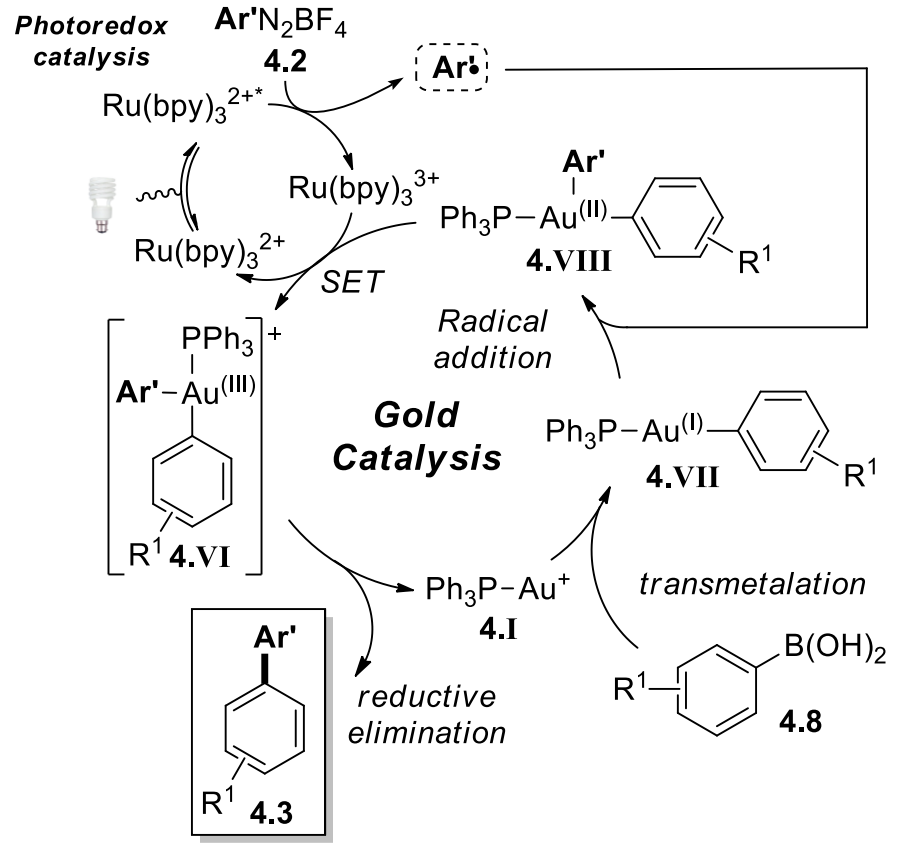


Scheme 4.8: Suzuki-type coupling reported by Fouquet[119]

Suzuki-type couplings are also possible using dual gold- and photoredox- catalysis. The coupling of boronic acids and diazonium salts through dual gold- and photoredox-catalysis was reported independently by the Lee group[118] (Scheme 4.7) and Fouquet[119] (Scheme 4.8). These reactions proceed in a similar manner as the dual gold and photoredox-catalysed Sonogashira-type couplings described in Scheme 4.6 with the boronic acid taking the place of the alkyne to give sp^2-sp^2 couplings. Unlike in the Sonogashira-type couplings (Scheme 4.6) where the activation of the C-H or C-Si can be assumed to be carried out by the gold(III) species, in the Suzuki-type couplings gold(I) or gold(III) catalysts could activate the C-B bond. This means that the C-B activation could occur before or after the oxidation of the gold(I) species. Further investigation by the Lee group led to the proposal of two possible catalytic cycles (Scheme 4.9 and 4.10). In the first catalytic cycle (Scheme 4.9), the aryl radical, generated by the photocatalysed breakdown of the diazonium salt, adds to the gold(I) catalyst **4.I** and then, after SET oxidation, the gold(III) species **4.III** undergoes transmetalation with the boronic acid to give intermediate **4.VI**. Reductive elimination of **4.VI** then provides the desired biaryl product **4.3** and regenerates the gold(I) catalyst **4.I**. Alternatively (Scheme 4.10), the gold(I) catalyst **4.I** can first add into the C-B bond[120] to give intermediate **4.VII** and then undergo radical addition followed by SET to provide the same gold(III) intermediate **4.VI** seen in Scheme 4.9. As in the "oxidation first" mechanism (Scheme 4.9) reductive elimination then delivers the product and completes the catalytic cycle.



Scheme 4.9: "Oxidation first" proposed mechanism[116]



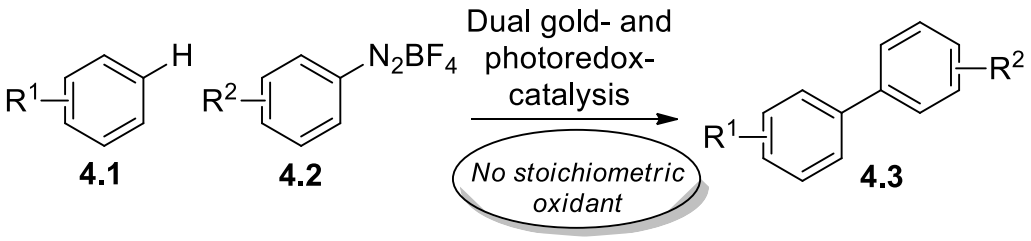
Scheme 4.10: "Transmetalation first" proposed mechanism[116]

Upon further investigation, the Lee group proposed that the mechanism by which the reaction proceeds is dependent on the catalyst which is used. When the neutral catalyst Ph_3PAuCl was used in the reaction the “oxidation first” mechanism (Scheme 4.9) is thought to be preferred. The “oxidation first” mechanism is suggested in this case as side product **4.9** is detected during stoichiometric NMR studies, implying the formation of **4.III** (Scheme 4.9). When the catalyst is switched to $Ph_3PAuNTf_2$, side product **4.9** is not detected suggesting the mechanism has changed and is reacting through the “transmetalation first” pathway (Scheme 4.10). The transmetallated intermediate **4.VII** is detected during stoichiometric NMR studies, providing evidence for the “transmetallation first” pathway in this case.

The examples discussed in this section show that photoredox can be used to access the Au(I)/Au(III) cycle under mild conditions and allows for a range of cross-coupling reactions with diazonium salts as one of the coupling partners. Prior to the work detailed in this chapter however, C(sp2)-H activation using dual gold- and photoredox-catalysis for aryl–aryl cross-couplings had not been reported.

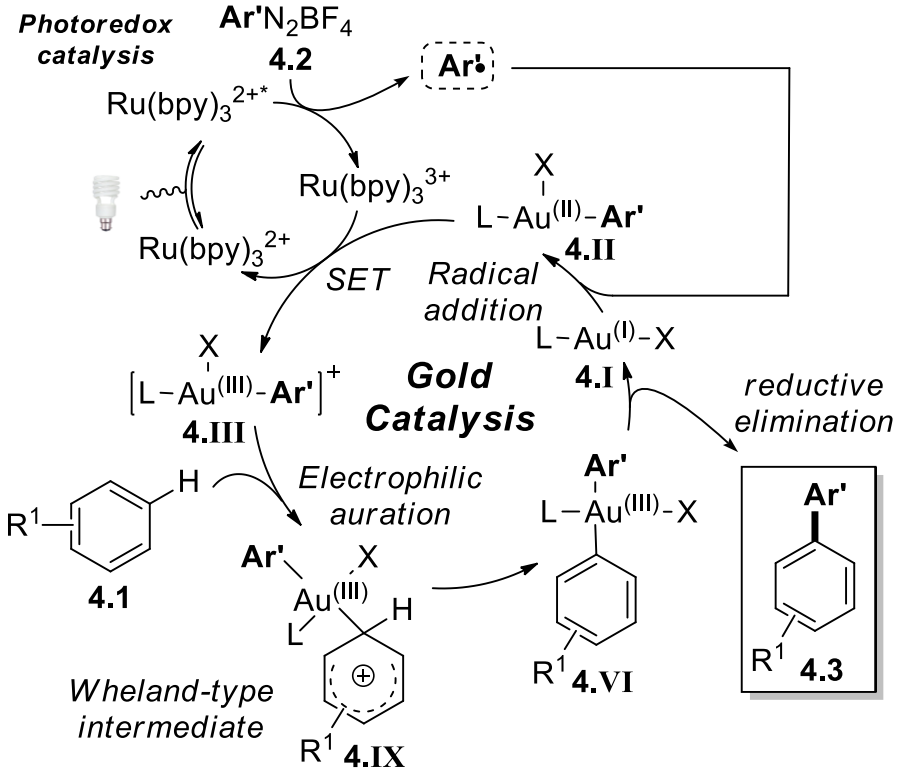
4.2 Project aims

The aim of the project was to develop the first dual gold- and photoredox-catalysed aryl–aryl cross-coupling reaction which proceeds through C-H activation and does not require a stoichiometric oxidant (Scheme 4.11).



Scheme 4.11: Desired aryl-aryl cross-coupling through dual gold and photoredox-catalysed C-H activation

Given the recent advances in gold-catalysed C-H activations and the development of dual gold- and photoredox- catalysis for cross-couplings (Section 4.1), the following catalytic cycle was envisaged (Scheme 4.12).



Scheme 4.12: Designed mechanism for aryl-aryl cross-coupling through C-H activation

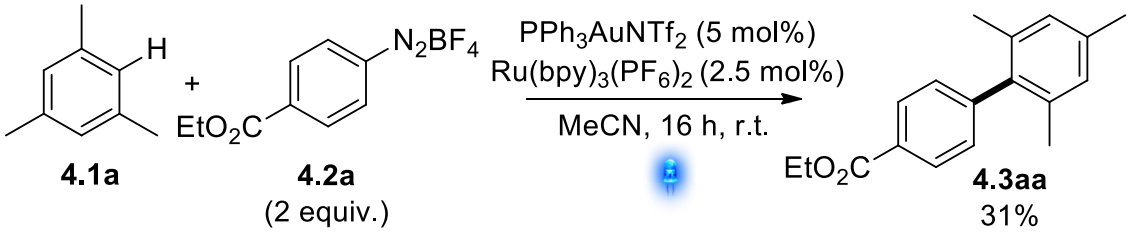
Photoredox- catalysis will be employed to access the Au(I)/Au(III) cycle through addition of the radical aryl from the diazonium salt **4.2** and subsequent SET. The gold(III) species **4.III** can then achieve C-H activation of a suitable arene **4.1** followed by reductive elimination to provide the biaryl product **4.3** (Scheme 4.12).

The dual gold- and photoredox-catalysed aryl–aryl cross-coupling methodology described will be a significant advancement as the mild conditions under which the Au(I)/Au(III) cycle is accessed allows oxidant-sensitive substrates to be subjected to the conditions and avoids the production of stoichiometric waste from the oxidant. Additionally, the use of gold C-H activation removes the need for prefunctionalisation of substrates and takes advantage of the regioselectivity seen in gold-catalysed C-H activations, removing the need for chelate assisted directing groups.

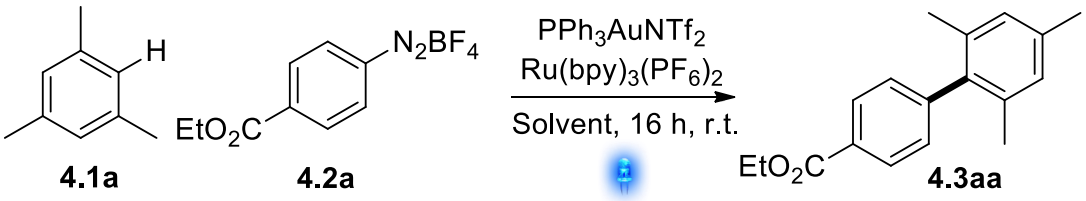
4.3 Results and Discussion

4.3.1 Optimisation

The starting point for the optimisation of the dual gold- and photoredox-catalysed C-H activation cross-coupling reaction was based on the Suzuki-type cross-coupling previously achieved in the group[116] (Scheme 4.7). Replacing the boronic acid **4.8** with mesitylene **4.1a** and removing the water, which was included to improve boronic acid solubility and assist transmetalation, gave our initial trial conditions (Scheme 4.13). The light source used for this reaction was also changed to the more easily standardised blue LEDs. To our delight, the conditions initially gave a promising yield of 31% (Scheme 4.13) and were successfully optimised (Table 4.1).



Scheme 4.13: Initial trial conditions[я]



Entry	Equiv. **4.1a**	Equiv. **4.2a**	PPh_3AuNTf_2 (mol%)	$Ru(bpy)_3(PF_6)_2$ (mol%)	Solvent	NMR yield (%)[a]
1[я]	1	2	5	2.5	MeCN	31%
2[я]	1	2	5	2.5	THF	ND
3[я]	1	2	5	2.5	DMF	ND
4[я]	1	2	5	2.5	Toluene	ND
5[я]	1	2	5	2.5	DCM	7%
6[я]	1	2	5	2.5	DCE	8%
7	1	2	5	2.5	MeOH	19%
8[я]	1	1	5	2.5	MeCN	51%
9	2	1	5	2.5	MeCN	61%
10	3	1	5	2.5	MeCN	67%

11	4	1	5	2.5	MeCN	68%
12[Я]	5	1	5	2.5	MeCN	52%
13	10	1	5	2.5	MeCN	54%
14[Я]	3	1	5	5	MeCN	43%
15[Я]	3	1	5	1	MeCN	63%
16	3	1	5	Eosin Y[b]	MeCN	62%
17	3	1	5	Fluorescein[b]	MeCN	58%
18	3	1	10	2.5	MeCN	81%
19[Я][c]	3	1	10	2.5	MeCN	51%
20[Я]	1	2	-	2.5	MeCN	<13%
21[Я]	1	2	5	-	MeCN	ND
22[Я][d]	1	2	5	2.5	MeCN	<9%

[a] Dimethylsulfone was used as the internal standard. [b] 2.5 mol%. [c] Reaction carried out under air. [d] No light. ND = not detected

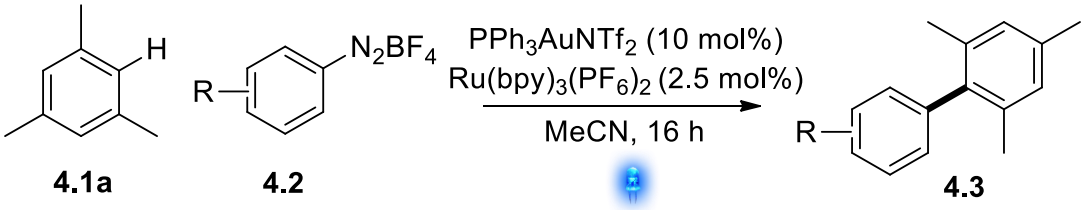
Table 4.1: Optimisation of reaction conditions

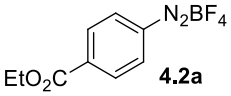
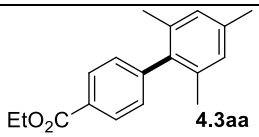
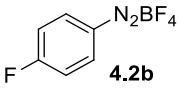
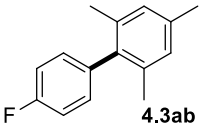
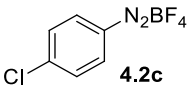
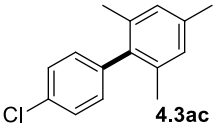
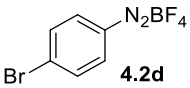
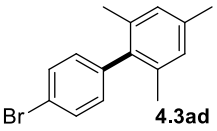
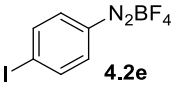
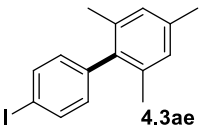
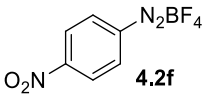
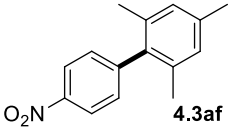
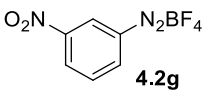
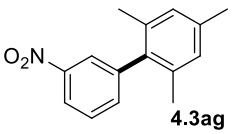
A scope of solvents showed that the solvent used in the trial reaction (MeCN, Entry 1, Table 4.1) outperformed the other solvents investigated (Entries 2-7, Table 4.1). Changing the equivalents so that the arene rather than the diazonium salt was in excess was investigated next with much more success (Entries 8-13, Table 4.1). The optimum number of equivalents of arene was found to be 3 or 4 (Entries 10 and 11, Table 4.1) with the yield dropping off when higher equivalents of arene were used (Entries 12 and 13, Table 4.1). The photocatalyst was investigated next with an increase in loading giving a decrease in yield (43% Entry 14 *vs.* 67% Entry 10, Table 4.1). With this in mind the loading of $Ru(bpy)_3(PF_6)_2$ was reduced, however a slight decrease in yield was observed (63% Entry 15 *vs.* 67% Entry 10, Table 4.1). Pleasingly, the organic photocatalysts Eosin Y and Fluorescein offer a viable alternative (62% and 58% respectively, Entries 16 and 17, Table 4.1) to the more expensive ruthenium catalyst $Ru(bpy)_3(PF_6)_2$ (67%, Entry 10, Table 4.1). Finally, the gold catalyst loading was increased to 10 mol% to give an optimised NMR yield of 81% (Entry 18, Table 4.1). As expected, the yield of the reaction was found to drop significantly when the reaction was not carried out under an inert atmosphere (51%, Entry 19, Table 4.1). Other control reactions carried out during the optimisation process showed that omission of

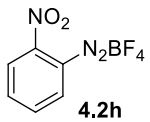
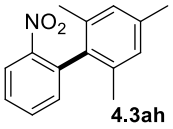
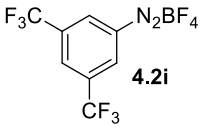
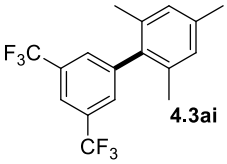
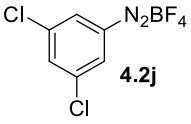
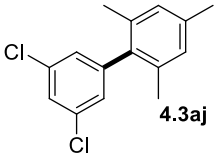
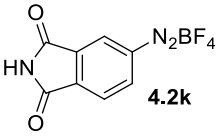
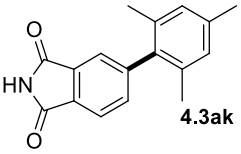
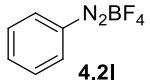
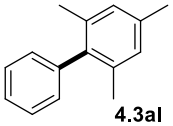
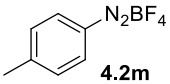
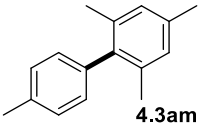
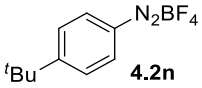
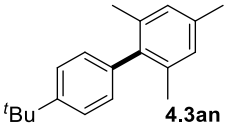
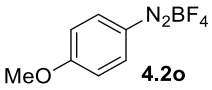
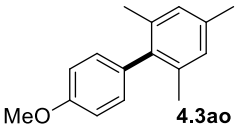
the gold or ruthenium catalysts or the light was detrimental to the reaction (Entries 20-22, Table 4.1).

4.3.2 Diazonium salt scope

With optimised conditions in hand (Entry 18, Table 4.1) an investigation into the scope of the reaction commenced (Table 4.2).



Entry	Diazonium salt	Cond.	Equiv. **4.1a**	Temp.	Product	Yield[a]
1	 **4.2a**	A	3	r.t.	 **4.3aa**	73%
2	 **4.2b**	A	3	r.t.	 **4.3ab**	80%
3	 **4.2c**	A	3	r.t.	 **4.3ac**	63%
4	 **4.2d**	A	3	r.t.	 **4.3ad**	73%
5	 **4.2e**	A	3	r.t.	 **4.3ae**	50%
6	 **4.2f**	A B	3 3	r.t. 50 °C	 **4.3af**	57% 62%
7	 **4.2g**	A	3	r.t.	 **4.3ag**	59%

8	 **4.2h**	A	3	r.t.	 **4.3ah**	37%
9	 **4.2i**	A B C	3 3 10	r.t. 50 °C 50 °C	 **4.3ai**	48% 50% 60%
10	 **4.2j**	A C	3 10	r.t. 50 °C	 **4.3aj**	41% 44%
11	 **4.2k**	A	3	r.t.	 **4.3ak**	67%
12	 **4.2l**	A	3	r.t.	 **4.3al**	62%
13	 **4.2m**	A	3	r.t.	 **4.3am**	48%
14	 **4.2n**	A	3	r.t.	 **4.3an**	48%
15	 **4.2o**	A	3	r.t.	 **4.3ao**	<26%[b]

[a] Isolated yield. [b] Yield of impure product

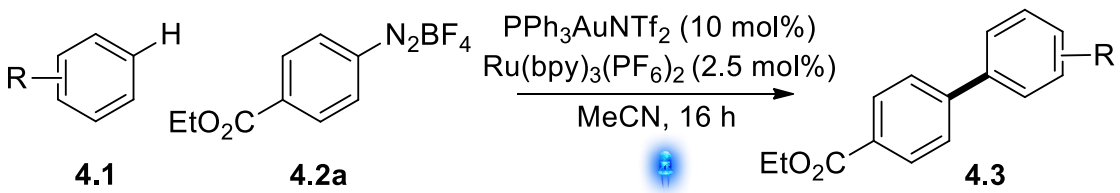
Table 4.2: Diazonium salt scope

Under the optimised conditions, mesitylene **4.1a** was reacted with a range of aryl diazonium salts **4.2**. The fluoro-, chloro-, and bromo- substituted aryl diazonium salts were subjected to our conditions first and reacted well giving the desired products **4.3ab**-**4.3ad** in good yields (80%, 63% and 73% respectively, Entries 2-4, Table 4.2). The final halogenated diazonium salt investigated, iodo-substituted **4.2e**, gave a slightly lower yield (**4.3ae**, 50%, Entry 5, Table 4.2) presumably due to the more labile C-I bond. Pleasingly though, *para*- and *meta*- nitro substituted substrates **4.2f** and **4.2g** reacted smoothly (**4.3af** and **4.3ag**, 57% (cond. A) and 59%, Entry 6 and 7, Table 4.2)

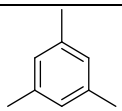
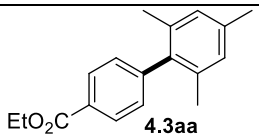
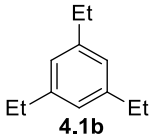
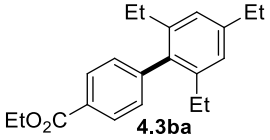
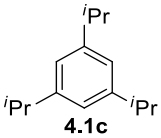
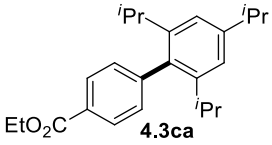
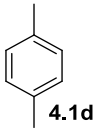
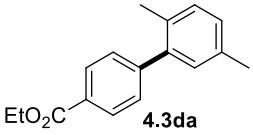
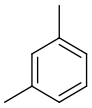
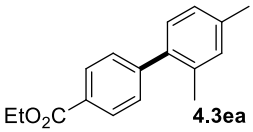
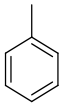
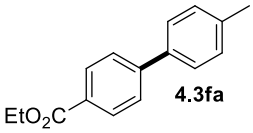
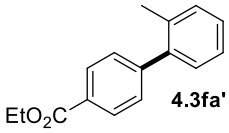
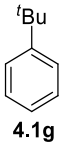
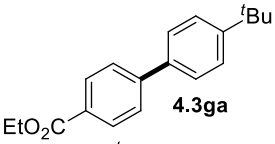
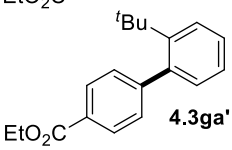
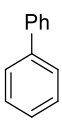
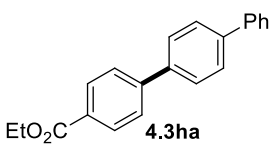
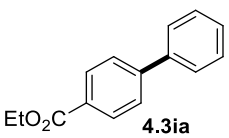
with **4.3af** being obtained in a slightly higher yield when reacted at 50 °C (62% (cond. B), Entry 6, Table 4.2). Understandably, moving to the *ortho*- substituted diazonium salt **4.2h** gave a drop in yield for the reaction (**4.3ah**, 37%, Entry 8, Table 4.2) presumably due to steric hindrance. Unfortunately, the poorer yield of *ortho*-substituted **4.3ah** could not be improved by raising the temperature of the reaction. Disubstituted and electron-poor **4.2i** and **4.2j** were targeted next. However, the yields under conditions A were initially disappointing (**4.3ai** and **4.3aj**, 48% and 41% (cond. A), Entries 9 and 10, Table 4.2) and raising the reaction temperature only resulted in an increase in diazonium salt homocoupling (**4.3ai**, 50% (cond. B), Entry 9, Table 4.2). However, to our delight, when the equivalents of mesitylene were also increased (Conditions C) the yield of biaryl **4.3ai** was raised to 60% (cond. C, Entry 9, Table 4.2). Disappointingly, when substrate **4.2j** was subjected to conditions C, the increase in yield of **4.3aj** was much more modest (44%, Entry 10, Table 4.2). Next, slightly electron-poor and electroneutral substrates **4.2k** and **4.2l** were investigated and their respective products obtained in good yields (**4.3ak** and **4.3al**, 67% and 62%, Entries 11 and 12, Table 4.2), however, the yield of the reaction dropped when moving to more electron-rich diazonium salts (**4.3am** and **4.3an**, 48% and 48%, Entries 13 and 14, Table 4.2). Unfortunately, increasing the temperature and equivalents of mesitylene did not improve the yield for these substrates (**4.2m** and **4.2n**) and the methoxy-substituted diazonium salt **4.2o** was found to be much less suited to the reaction, providing impure **4.3ao** in a low yield (<26%, Entry 15, Table 4.2).

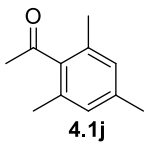
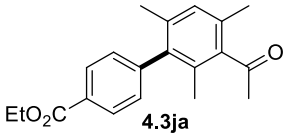
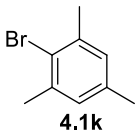
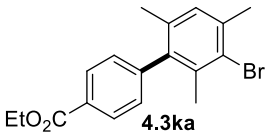
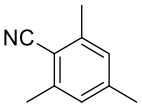
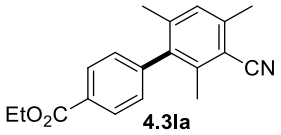
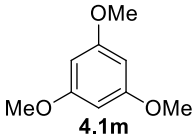
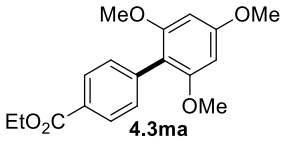
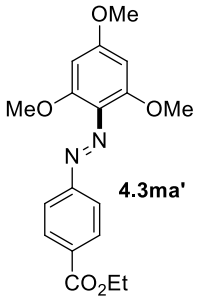
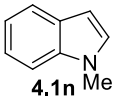
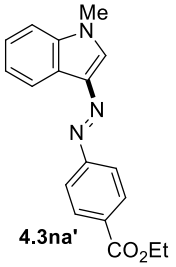
4.3.3 Arene scope

The arene scope of the reaction was investigated next, targeting electron-rich and electron neutral arenes. As previously discussed, electron-poor arenes are unsuited to the electrophilic aromatic substitution step required for the reaction to proceed (see Section 4.1.1).



4.1 **4.2a** **4.3**

Entry	Arene	Cond.	Equiv. **4.1a**	Temp.	Major product	Yield[a]
1	 **4.1a**	A	3	r.t.	 **4.3aa**	73%
2	 **4.1b**	A	3	r.t.	 **4.3ba**	35%
3	 **4.1c**	A	3	r.t.	 **4.3ca**	<5%[b]
4	 **4.1d**	A C	3 10	r.t. 50 °C	 **4.3da**	50%[b] 82%
5	 **4.1e**	C	10	50 °C	 **4.3ea**	82%
6	 **4.1f**	C	10	50 °C	 **4.3fa**  **4.3fa'**	76%[c] **4.3fa**:**4.3fa'** 2.7:1 56% **4.3fa**[d]
7	 **4.1g**	C	10	50 °C	 **4.3ga**  **4.3ga'**	71%[c] **4.3ga**:**4.3ga'** 5.7:1
8	 **4.1h**	C	10	50 °C	 **4.3ha**	56%
9	 **4.1i**	C	10	50 °C	 **4.3ia**	58%

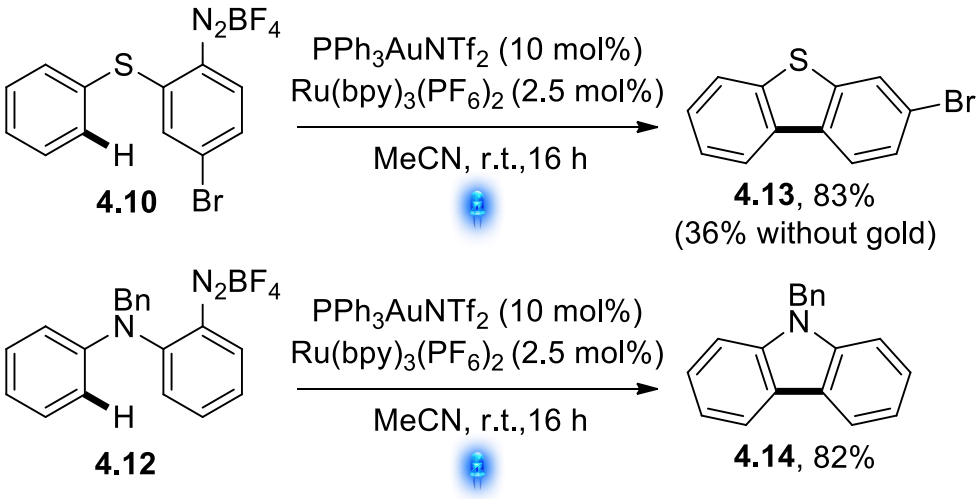
10	 **4.1j**	C	10	50 °C	 **4.3ja**	52%
11	 **4.1k**	C	10	50 °C	 **4.3ka**	57%
12	 **4.1l**	C	10	50 °C	 **4.3la**	37%
13	 **4.1m**	C	10	50 °C	 **4.3ma**  **4.3ma'**	trace[b] **4.3ma** <50%[e]
14	 **4.1n**	C	10	50 °C	 **4.3na'**	92%[b] (**4.3na** ND)

[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] Combined isolated yield of both isomers obtained. [d] Isolated yield of major product. [e] Yield of impure product. ND = Not detected.

Table 4.3: Arene scope[Я]

Although the already fairly sterically hindered mesitylene performed well under our conditions, when larger alkyl groups are used in place of the methyl groups of mesitylene the yield of the reaction dropped of significantly (**4.3ba** and **4.3ca**, 35% and <5%, Entries 2 and 3, Table 4.3). *Para*-xylene **4.1d** was investigated next but disappointingly gave a NMR yield of only 50% under conditions A (**4.3da**, Entry 4, Table 4.3). To our delight, this could be improved greatly by increasing the temperature to 50 °C and the equivalents of arene to 10 (Conditions C) (**4.3da**, 82%, Entry 4, Table 4.3). Conditions C were found to be much more general and were applied to the remainder of the substrate scope.

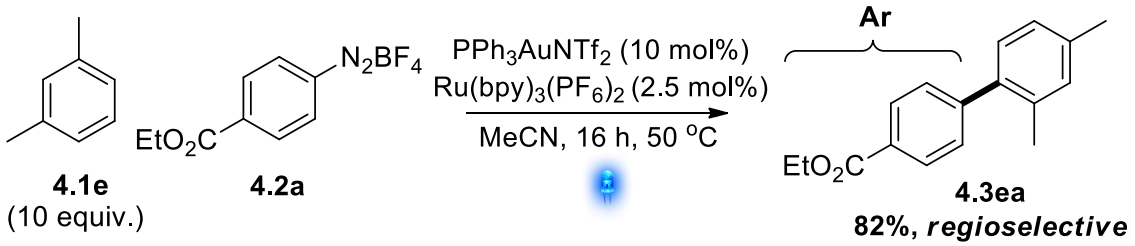
The regioselectivity conferred by the gold-catalysed C-H activation step was examined next and pleasingly showed perfect regioselectivity giving **4.3ea** as the only product, in excellent yield (82%, Entry 5, Table 4.3). The high yield and selectivity achieved for **4.3ea** is in stark contrast to the photocatalyst-only approach previously reported,[121] showing the importance of the gold catalyst in this methodology (see Section 4.3.4). Toluene **4.1f** and *tert*-butylbenzene **4.1g** were also subjected to the reaction conditions, predictably forming a mixture of *para*- and *ortho*- substituted products (2.7:1 and 5.7:1 respectively, Entries 6 and 7, Table 4.3). Thankfully, the overall yields for the two reactions are good (**4.3fa** and **4.3ga**, 76% and 71%, Entries 6 and 7, Table 4.3) and the major *para*-isomer of **4.3fa** can be isolated in a 56% yield. To our delight, biphenyl **4.1h** reacts exclusively at the *para*-position giving tricyclic **4.3ha** in good yield (56%, Entry 8, Table 4.3) and benzene **4.1i** also reacts smoothly (**4.3ia**, 58%, Entry 9, Table 4.3). Substituted mesitylene substrates **4.1j** and **4.1k** also reacted well despite bearing electron-withdrawing groups (**4.3ja** and **4.3ka**, 52% and 57%, Entries 10 and 11, Table 4.3). However, as predicted, moving to more strongly electron withdrawing substituents does lower the yield of the reaction (**4.3la**, 37%, Entry 12, Table 4.3). Unfortunately, very electron-rich substrates are unsuited to the reaction conditions due to the competing azo coupling reaction[122, 123] (**4.3ma'** and **4.3na'**, Entries 13 and 14, Table 4.3).



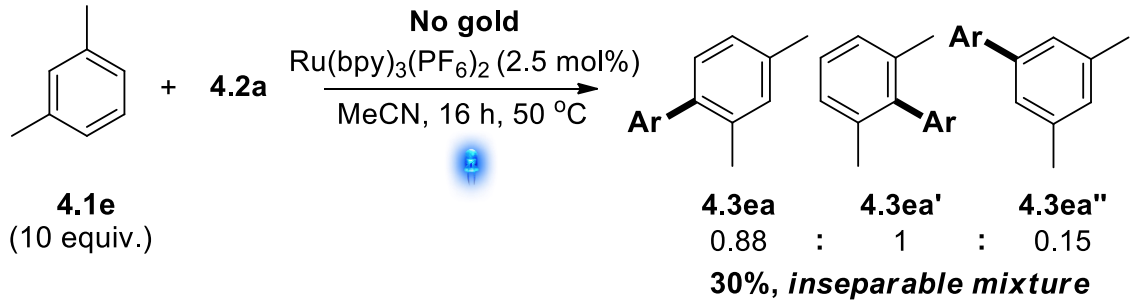
Scheme 4.14: Intramolecular examples[Я]

To our delight, the intramolecular version of the reaction was found to proceed with excellent yield (Scheme 4.14) and with no oxidation of the sulfide or benzylic positions of the substrates. The reactions' tolerance of these readily oxidizable moieties is due to the use of mild photoredox conditions, rather than harsh stoichiometric oxidants previously used in the gold-catalysed C-H activations.

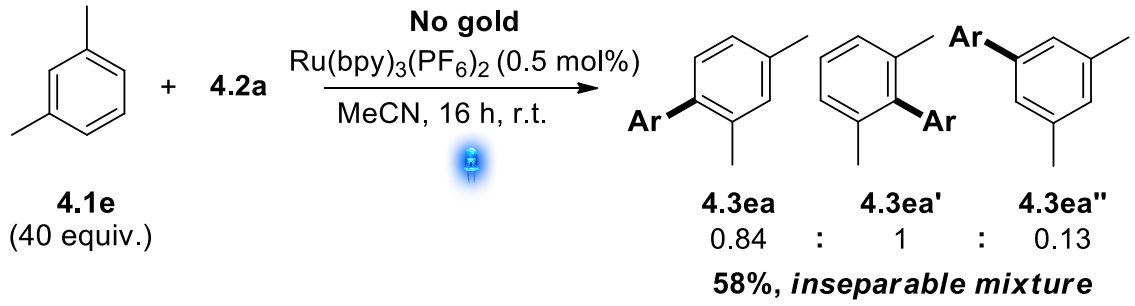
4.3.4 Investigation into regioselectivity



Scheme 4.15: Our optimised dual gold- and photoredox- catalysed conditions[Я]



Scheme 4.16: Our optimised conditions without gold catalyst[Я]

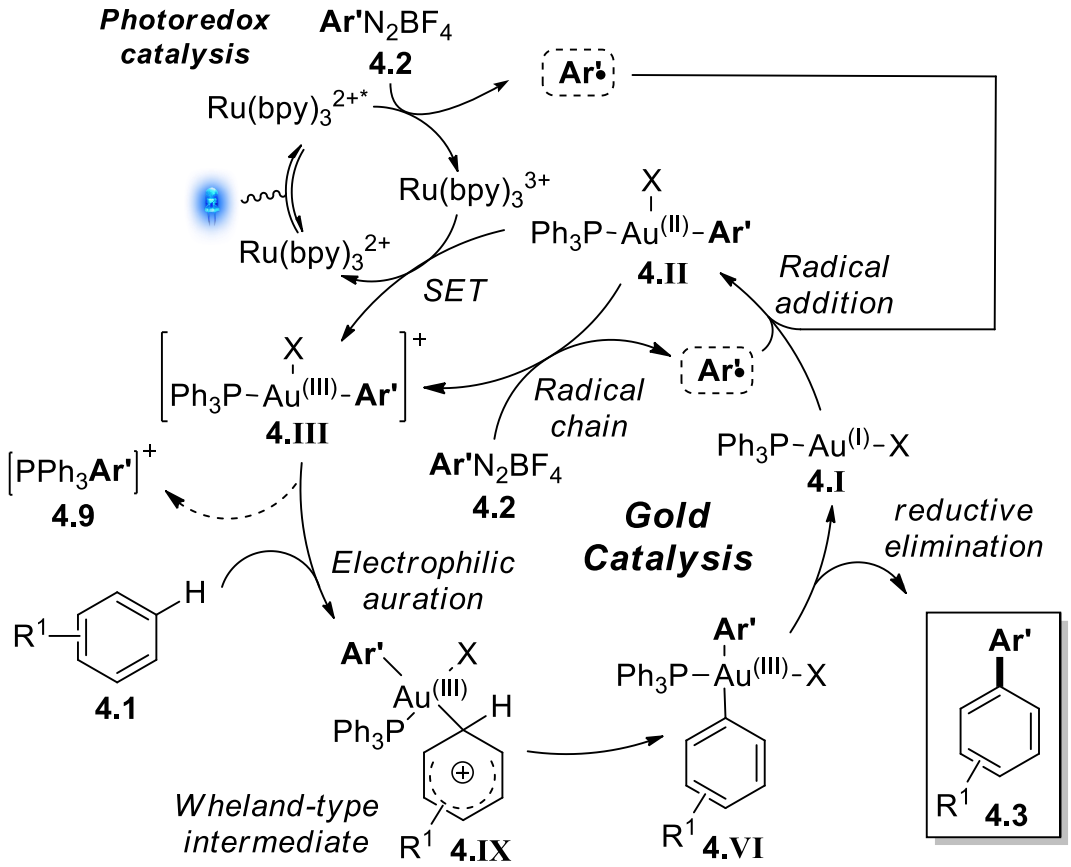


Scheme 4.17: Reported photoredox only conditions[Я 121]

One of the main advantages of gold-catalysed C-H activation is the regioselectivity conferred in the C-H activation step. This is demonstrated very clearly in the arylation of *meta*-xylene which occurs totally selectively and in high yield under our dual gold- and photoredox-catalysed conditions (82%, Scheme 4.15). This is in stark contrast to

the same conditions without the gold catalyst which give a much lower yield of an inseparable mixture of all three possible isomers (30%, Scheme 4.16). This shows conclusively that the reaction developed is a dual gold- and photoredox-catalysed reaction and not a photocatalysis-only process. Also, the poor regioselectivity observed without the gold catalyst shows that the gold-catalysed C-H activation step is crucial to obtaining the excellent regioselectivity observed under our conditions. Comparison with a reported photocatalyst-only reaction (Scheme 4.17) shows that under more optimised conditions (using a larger excess of arene **4.1e**) the yield can be improved. However, the combined yield is still substantially lower under the reported photocatalyst-only conditions compared to our dual gold- and photoredox-catalysed methodology (58% *vs.* 82%) and crucially the regioselectivity observed is much poorer.

4.3.5 Proposed mechanism



Scheme 4.18: Proposed mechanism

The dual gold- and photoredox- catalytic cycle is thought to begin with the excitation of the ruthenium photocatalyst, which can then reduce the diazonium salt **4.2** to

generate the aryl radical. The gold(I) catalyst then undergoes radical addition with the aryl radical to give gold complex **4.II,** which can undergo single electron transfer (SET) to regenerate the ruthenium photocatalyst and provide the crucial gold(III) intermediate **4.III**. Alternatively, the gold complex **4.II** could undergo SET to another diazonium salt **4.2** to generate another aryl radical. This aryl radical can in turn add to another gold(I) catalyst, thereby regenerating the gold complex **4.II** and allowing for radical chain propagation which does not require the photocatalytic cycle to turn over. Quantum yield calculations carried out on the related dual gold- and photoredox-catalysed alkyne coupling reaction[114] (Scheme 4.4) show that this radical chain pathway is possible under similar conditions. The gold(III) intermediate **4.III**, which is known to be formed in the reaction due to NMR detection of **4.9**,[111, 116] can then undergo the crucial C-H activation step. This step confers regioselectivity to the product as it occurs through the Wheland-type intermediate shown (Scheme 4.18). Finally reductive elimination provides the biaryl product **4.3** and regenerates the gold(I) catalyst **4.I**.

Consideration of the proposed mechanism can help to explain some of the trends seen in the scope of the reaction. Firstly, as predicted, electron-poor arenes are not suited to this reaction (Section 4.3.3) as the crucial C-H activation step occurs through electrophilic auration. Also, electron-rich diazonium salts (**4.2m**-**4.2o**, Section 4.3.2) do not perform as well in the reaction. This could be because the gold(III) intermediate **4.III** will be less electron deficient and so less reactive with an electron-rich aryl substituent.

4.4 Conclusions

Dual gold- and photoredox- catalysed aryl–aryl cross-coupling through C–H activation has been achieved for the first time. This work also constitutes the first gold-catalysed C-H activation of an arene for aryl–aryl cross-coupling which does not require stoichiometric oxidant, cited as one of the major limitations in gold-catalysed C–H activations.[101] The avoidance of stoichiometric oxidant allows the scope to be expanded to oxidant sensitive substrates and also avoids the production of stoichiometric waste. The other major limitation in the field of gold-catalysed C–H activation reactions is the restricted arene scope. This limitation is due to electron-poor arenes being unsuited to the electrophilic auration step of the catalytic cycle and could not be overcome in this project. As a result, the arene scope of the reaction is limited to electron-rich and electron neutral substrates, however, it did show good functional group tolerance. Unfortunately, competing azo-coupling meant that very electron-rich arenes such as trimethoxybenzene were also unsuited to the reaction, but pleasingly the intramolecular version of the reaction shows great promise. Gratifyingly, the diazonium scope was much broader with electron-poor diazonium salts being higher yielding in the reaction.

A short investigation into the regioselectivity observed in the reaction found that, as suspected, the gold C-H activation step confers regioselectivity to the product. When the gold catalyst was removed from the reaction, the yield dropped and the previously excellent regioselectivity was lost. Although the yield could be partially recovered under previously reported photocatalyst-only conditions,[121] the regioselectivity was still very poor. This demonstrates that the methodology developed is indeed a dual gold- and photoredox-catalysed process and shows the importance of the gold-catalysed C-H activation step for conferring regioselectivity in this reaction.

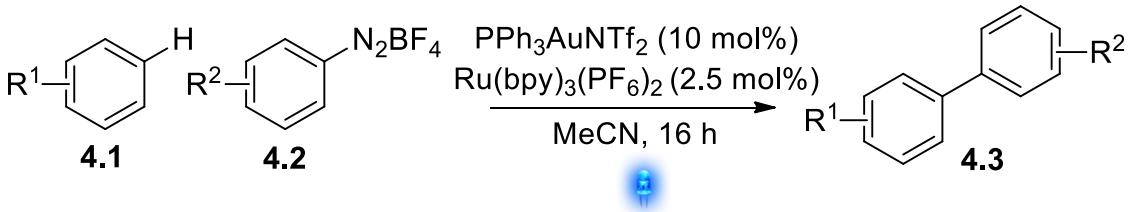
4.5 Experimental

4.5.1 General considerations

^{1}H NMR spectra was recorded on Bruker AV 300 and AV 400 spectrometers at 300 and 400 MHz respectively and referenced to residual solvent. ^{13}C NMR spectra were recorded using the same spectrometers at 75 and 100 MHz respectively. Chemical shift data are quoted in parts per million (ppm) and are referenced to tetramethylsilane (TMS) or to residual solvent peaks ($CDCl_3$ at δ_H 7.26). *J* values are given in Hz and s, d, dd, dt, ddt, dtd, t, td, tt, q, qd, qt, p and m abbreviations correspond to singlet, doublet, doublet of doublet, doublet of triplet, doublet of doublet of triplet, doublet of triplet of doublet, triplet, triplet of doublet, triplet of triplet, quartet, quartet of doublet, quartet of triplet, quintet and multiplet respectively. Mass spectra were obtained at the EPSRC National Mass Spectrometry Service Centre in Swansea. Infrared spectra were obtained on Perkin-Elmer Spectrum 100 FT-IR Universal ATR Sampling Accessory, deposited neat or as a chloroform solution to a diamond/ZnSe plate. Flash column chromatography was carried out using silica gel 60 from Fisher Chemicals or Silicagel 60A from Fluorochem and TLC was performed using Merck silica gel 60 F254 pre-coated sheets and visualised by UV (254 nm) or stained by the use of aqueous acidic $KMnO_4$ or aqueous acidic ceric ammonium molybdate as appropriate. Chemicals were purchased from Sigma-Aldrich, Acros, Apollo Scientific, Fisher, Fluorochem and Manchester Organics chemical companies and used without further purification unless otherwise stated. MeCN was dried using an MBRAUN SPS-800 solvent purification system.

Unless otherwise stated, all dual gold and photoredox reactions were carried out under inert atmosphere using Schlenk techniques. Prior to each catalytic run, the reaction vessel was wrapped in aluminium foil and the mixture was degassed in the dark through three freeze-thaw (1 min)-pump cycles. The foil was then removed, and light irradiation was performed using blue LEDs (1.5 Watt/foot).

4.5.2 Dual gold- and photoredox- catalysed aryl–aryl cross-couplings

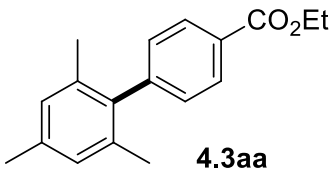


General procedure A: Diazonium salt **4.2** (0.1 mmol), PPh_3AuNTf_2 (7.8 mg, 0.01 mmol, 10 mol%) and $Ru(bpy)_3(PF_6)_2$ (2.2 mg, $2.5x10^{-3}$ mmol) were added to a nitrogen or argon backfilled Schlenk tube and wrapped in aluminium foil before MeCN (1 ml) was added, and the mixture was degassed using 3 freeze-pump-thaw cycles. The mixture was allowed to warm to r.t. and arene **4.1** (3 equiv.) was added. The foil was removed and the reaction mixture was stirred for 16 h at r.t., under blue LED light irradiation. The mixture was then diluted with EtOAc (10 ml) and washed with distilled water. The aqueous phase was extracted with EtOAc and the combined organic phases were washed with brine, dried over magnesium sulfate and concentrated under vacuum before purification by column chromatography to give product **4.3**.

General procedure B: As in general procedure A, but the reaction was heated to 50 °C instead of r.t.

General procedure C: As in general procedure A, but 10 equiv. of arene **1** was used and the reaction was heated to 50 °C instead of r.t.

Ethyl 2',4',6'-trimethyl-[1,1'-biphenyl]-4-carboxylate (4.3aa)



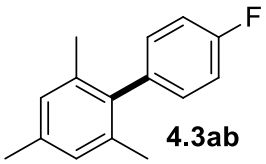
4.3aa

General procedure A followed and crude purified by column chromatography (eluent: 50:1 petrol 40-60 °C/EtOAc) to yield product **4.3aa** as a light yellow oil (19.6 mg, 0.073 mmol, 73%).

R_F 0.21 (50:1 petrol 40-60 °C/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 - 8.17 (2H, m, Ar-H), 7.23 - 7.29 (2H, m, Ar-H), 6.98 (2H, s, Ar-H), 4.42 (2 H, q, *J* = 7.3 Hz, CH_2), 2.37

(3H, s, CH_3), 2.02 (6H, s, $2CH_3$), 1.45 (3 H, t, *J* = 7.3 Hz, CH_3); NMR data matches literature values[124] and characterisation carried out by Vincent Gauchot

4'-Fluoro-2,4,6-trimethyl-1,1'-biphenyl (4.3ab)

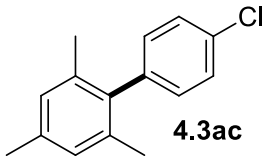


4.3ab

General procedure A followed and crude purified by column chromatography (eluent: petrol 40-60 °C) to yield product **4.3ab** as a light yellow oil (17.2 mg, 0.080 mmol, 80%).

R_F 0.27 (petrol 40-60 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 – 7.16 (4H, m, Ar-H), 6.98 (2H, s, Ar-H), 2.37 (3H, s, CH_3), 2.04 (6H, s, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8 (d, *J* = 244.8 Hz, CF), 138.1 (C), 137.0 (d, *J* = 3.5 Hz, CCHCHCF), 136.9 (C), 136.3 (2C), 131.0 (d, *J* = 7.8 Hz, CHCHCF), 128.3 (2CH), 115.4 (d, *J* = 21.1 Hz, CHCF), 21.2 (CH_3), 20.9 ($2CH_3$); Found (TOF MS ASAP+) $[M]^+$ 214.1158, $C_{15}H_{15}F$ requires 214.1158; NMR data matches literature values.[125]

4'-Chloro-2,4,6-trimethyl-1,1'-biphenyl (4.3ac)

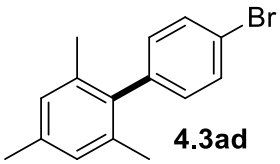


4.3ac

General procedure A followed and crude purified by column chromatography (eluent: petrol 40-60 °C) to yield product **4.3ac** as a light yellow oil (14.6 mg, 0.063 mmol, 63%).

R_F 0.27 (petrol 40-60 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.43 (2H, m, Ar-H), 7.05 – 7.12 (2H, m, Ar-H), 6.95 (2H, s, Ar-H), 2.34 (3H, s, CH_3), 2.00 (6H, s, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5 (C), 137.7 (C), 136.9 (C), 135.9 (2C), 132.5 (C), 130.7 (2CH), 128.7 (2CH), 128.2 (2CH), 21.0 (CH_3), 20.7 ($2CH_3$); Found (TOF MS EI+) $[M]^+$ 230.0862, $C_{15}H_{15}Cl$ requires 230.0869; NMR data matches literature values.[126]

4'-Bromo-2,4,6-trimethyl-1,1'-biphenyl (4.3ad)

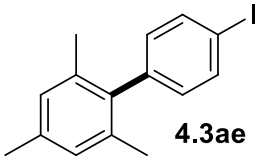


4.3ad

General procedure A followed and crude purified by column chromatography (eluent: petrol 40-60 °C) to yield product **4.3ad** as a light yellow oil (20.1 mg, 0.073 mmol, 73%).

R_F 0.29 (petrol 40-60 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.64 (2H, m, Ar-H), 7.02 – 7.13 (2H, m, Ar-H), 6.99 (2H, s, Ar-H), 2.37 (3H, s, CH_3), 2.04 (6H, s, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.0 (C), 137.9 (C), 137.1 (C), 135.9 (2C), 131.7 (2CH), 131.3 (2CH), 128.3 (2CH), 120.8 (C), 21.2 (CH_3), 20.9 ($2CH_3$); Found (TOF MS EI+) $[M]^+$ 274.0356, $C_{15}H_{15}Br$ requires 274.0357; NMR data matches literature values.[127]

4'-Iodo-2,4,6-trimethyl-1,1'-biphenyl (4.3ae)

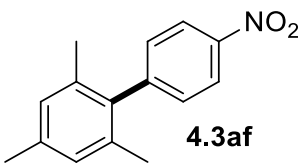


4.3ae

General procedure A followed and crude purified by column chromatography (eluent: petrol 40-60 °C) to yield product **4.3ae** as a light yellow oil (16.0 mg, 0.050 mmol, 50%).

R_F 0.28 (petrol 40-60 °C); ν_{max}/cm^{-1} 2918, 2853 (C-H), 1471 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.80 (2H, m, Ar-H), 6.96 (2H, s, Ar-H), 6.84 – 6.93 (2H, m, Ar-H), 2.33 (3H, s, CH_3), 2.00 (6H, s, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8 (C), 137.9 (C), 137.7 (2CH), 137.1 (C), 135.9 (2C), 131.6 (2CH), 128.3 (2CH), 92.3 (C), 21.2 (CH_3), 20.9 ($2CH_3$); Found (TOF MS EI+) $[M]^+$ 322.0225, $C_{15}H_{15}I$ requires 322.0219.

2,4,6-Trimethyl-4'-nitro-1,1'-biphenyl (4.3af)

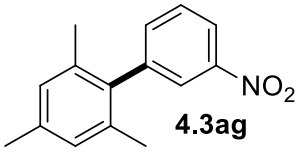


4.3af

General procedure A followed and crude purified by column chromatography (eluent: 50:1 petrol 40-60 °C/EtOAc) to yield product **4.3af** as a light yellow oil (15.0 mg, 0.062 mmol, 62%).

R_F 0.24 (50:1 petrol 40-60 °C/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 – 8.37 (2H, m, Ar-H), 7.29 – 7.40 (2H, m, Ar-H), 6.97 (2H, s, Ar-H), 2.35 (3H, s, CH_3), 1.99 (6H, s, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7 (C), 147.0 (C), 137.9 (C), 136.9 (C), 135.4 (2C), 130.6 (2CH), 128.5 (2CH), 123.9 (2CH), 21.2 (CH_3), 20.8 ($2CH_3$); Found (TOF MS ASAP+) $[M + H]^+$ 242.1181, $C_{15}H_{15}NO_2$ requires 242.1181; NMR data matches literature values.[126]

2,4,6-Trimethyl-3'-nitro-1,1'-biphenyl (4.3ag)

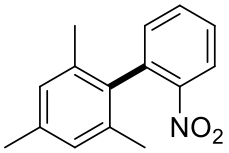


4.3ag

General procedure B followed and crude purified by column chromatography (eluent: 50:1 petrol 40-60 °C/EtOAc) to yield product **4.3ag** as a light yellow oil (14.4 mg, 0.059 mmol, 59%).

R_F 0.24 (50:1 petrol 40-60 °C/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 – 8.27 (1H, m, Ar-H), 8.02 – 8.07 (1H, m, Ar-H), 7.54 – 7.67 (1H, m, Ar-H), 7.42 – 7.54 (1H, m, Ar-H), 6.97 (2H, s, Ar-H), 2.35 (3H, s, CH_3), 1.99 (6H, s, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6 (C), 143.0 (C), 137.8 (C), 136.6 (C), 136.0 (CH), 135.7 (2C), 129.6 (CH), 128.6 (2CH), 124.6 (CH), 121.9 (CH), 21.2 (CH_3), 20.8 ($2CH_3$); Found (TOF MS ASAP+) $[M + H]^+$ 242.1179, $C_{15}H_{15}NO_2$ requires 242.1181; NMR data matches literature values.[128]

2,4,6-Trimethyl-2'-nitro-1,1'-biphenyl (4.3ah)

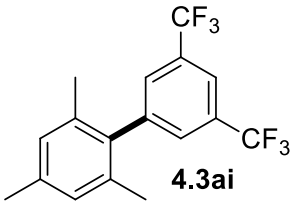


4.3ah

General procedure A followed and crude purified by column chromatography (eluent: 50:1 petrol 40-60 °C/EtOAc) to yield product **4.3ah** as a light yellow oil (8.8 mg, 0.037 mmol, 37%).

R_F 0.24 (50:1 petrol 40-60 °C/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 – 8.08 (1H, m, Ar-H), 7.59 – 7.74 (1H, m, Ar-H), 7.39 – 7.59 (1H, m, Ar-H), 7.17 – 7.30 (1H, m, Ar-H), 6.91 (2H, s, Ar-H), 2.31 (3H, s, CH_3), 1.95 (6H, s, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5 (C), 137.6 (C), 136.0 (C), 135.6 (2C), 134.3 (C), 133.0 (CH), 132.2 (CH), 128.29 (2CH), 128.28 (CH), 124.3 (CH), 21.2 (CH_3), 20.5 ($2CH_3$); Found (TOF MS ASAP+) $[M + H]^+$ 242.1179, $C_{15}H_{15}NO_2$ requires 242.1181; NMR data matches literature values.[129]

2,4,6-Trimethyl-3',5'-bis(trifluoromethyl)-1,1'-biphenyl (4.3ai)

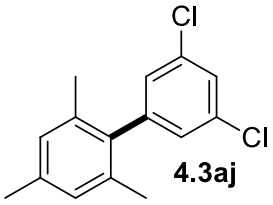


4.3ai

General procedure C followed and crude purified by column chromatography (eluent: petrol 40-60 °C) to yield product **4.3ai** as a light yellow oil (19.8 mg, 0.060 mmol, 60%).

R_F 0.32 (petrol 40-60 °C); ν_{max}/cm^{-1} 2924 (C-H), 1616, 1464 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (1H, s, Ar-H), 7.63 (2H, s, Ar-H), 6.97 (2H, s, Ar-H), 2.34 (3H, s, CH_3), 1.98 (6H, s, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5 (C), 138.2 (C), 136.0 (C), 135.7 (2C), 131.95 (q, J = 33.2 Hz, 2$\underline{C}CF_3$), 129.9 (m, CH), 128.7 (2CH), 123.5 (q, J = 272.8 Hz, CF_3) 120.9 (m, CH) 21.03 (CH_3), 20.71 ($2CH_3$); Found (TOF MS EI+) $[M]^+$ 332.1001, $C_{17}H_{14}F_6$ requires 332.1000.

3',5'-Dichloro-2,4,6-trimethyl-1,1'-biphenyl (4.3aj)

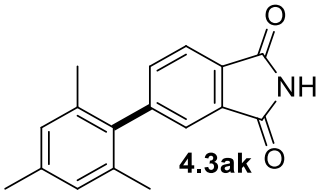


4.3aj

General procedure C followed and crude purified by column chromatography (eluent: petrol 40-60 °C) to yield product **4.3aj** as a light yellow oil (11.6 mg, 0.044 mmol, 44%). R_F 0.29 (petrol 40-60 °C); ν_{max}/cm^{-1} 2919, 2855 (C-H), 1613, 1586, 1556 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (1H, t, J = 1.9 Hz, Ar-H), 7.04 (2H, d, J = 1.9 Hz, Ar-H), 6.93 (2H, s, Ar-H), 2.32 (3H, s, CH_3), 2.01 (6H, s, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4 (C),

137.6 (C), 136.5 (C), 135.7 (2C), 135.1 (2C), 128.4 (2CH), 128.1 (2CH), 127.0 (CH), 21.2 (CH_3), 20.8 ($2CH_3$); Found (TOF MS EI+) $[M]^+$ 264.0463, $C_{15}H_{14}Cl_2$ requires 264.0472.

5-Mesitylisoindoline-1,3-dione (4.3ak)

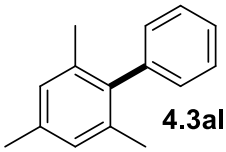


4.3ak

General procedure A followed and crude purified by column chromatography (eluent: 10:1 petrol 40-60 °C/EtOAc) to yield product **4.3ak** as a light yellow oil (17.8 mg, 0.067 mmol, 67%).

R_F 0.23 (10:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 3196 (N-H), 2919 (C-H), 1765, 1727, 1699 (C=O), 1616, 1469 (C-C Ar); ^1H NMR (300 MHz, $CDCl_3$) δ 8.14 (1H, broad s, N-H), 7.92 (1H, dd, *J* = 7.6, 0.5 Hz, Ar-H), 7.67 (1H, dd, *J* = 1.4, 0.5 Hz, Ar-H), 7.53 (1H, dd, *J* = 7.6, 1.4 Hz, Ar-H), 6.97 (2H, s, Ar-H), 2.34 (3H, s, CH_3), 1.98 (6H, s, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3 (C), 168.2 (C), 148.6 (C), 137.9 (C), 136.9 (C), 135.7 (CH), 135.4 (2C), 133.2 (C), 131.1 (C), 128.6 (2CH), 124.9 (CH), 123.9 (CH), 21.2 (CH_3), 20.8 ($2CH_3$); Found (FTMS p NSI+) $[M + H]^+$ 266.1177, $C_{17}H_{16}NO_2$ requires 266.1176.

2,4,6-Trimethyl-1,1'-biphenyl (4.3al)

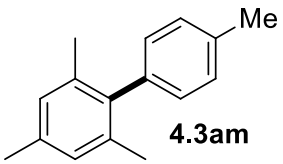


4.3al

General procedure A followed and crude purified by column chromatography (eluent: petrol 40-60 °C) to yield product **4.3al** as a light yellow oil (12.3 mg, 0.062 mmol, 62%).

R_F 0.26 (petrol 40-60 °C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.47 (2H, m, Ar-H), 7.29 – 7.37 (1H, m, Ar-H), 7.11 – 7.18 (2H, m, Ar-H), 6.96 (2H, s, Ar-H), 2.35 (3H, s, CH_3), 2.02 (6H, s, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2 (C), 139.2 (C), 136.7 (C), 136.1 (2C), 129.4 (CH), 128.5 (2CH), 128.2 (2CH), 126.6 (CH), 21.2 (CH_3), 20.9 ($2CH_3$); Found (TOF MS EI+) $[M]^+$ 196.1252, $C_{15}H_{16}$ requires 196.1252; NMR data matches literature values.[126]

2,4,4',6-Tetramethyl-1,1'-biphenyl (4.3am)

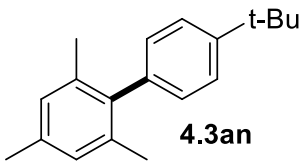


4.3am

General procedure A followed and crude purified by column chromatography (eluent: petrol 40-60 °C) to yield product **4.3am** as a light yellow oil (12.8 mg, 0.048 mmol, 48%).

R_F 0.28 (petrol 40-60 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 – 7.25 (2H, m, Ar-H), 7.00 – 7.07 (2H, m, Ar-H), 6.94 (2H, s, Ar-H), 2.41 (3H, s, CH_3), 2.34 (3H, s, CH_3), 2.02 (6H, s, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2 (C), 138.1 (C), 136.5 (C), 136.3 (2C), 136.1 (C), 129.3 (2CH), 129.2 (2CH), 128.2 (2CH), 21.4 (CH_3), 21.2 (CH_3), 20.9 ($2CH_3$); Found (TOF MS EI+) $[M]^+$ 210.1411, $C_{16}H_{18}$ requires 210.1409; NMR data matches literature values.[130]

4'-(Tert-butyl)-2,4,6-trimethyl-1,1'-biphenyl (4.3an)

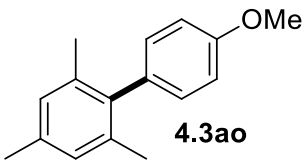


4.3an

General procedure A followed and crude purified by column chromatography (eluent: petrol 40-60 °C) to yield product **4.3an** as a light yellow oil (15.6 mg, 0.048 mmol, 48%).

R_F 0.30 (petrol 40-60 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.44 (2H, m, Ar-H), 7.03 – 7.11 (2H, m, Ar-H), 6.95 (2H, s, Ar-H), 2.34 (3H, s, CH_3), 2.03 (6H, s, $2CH_3$), 1.38 (9H, s, $3CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.28 (C), 139.20 (C), 138.00 (C), 136.48 (C), 136.39 (2C), 129.00 (2CH), 128.12 (2CH), 125.25 (2CH), 34.65 (C), 31.61 ($3CH_3$), 21.16 (CH_3), 20.89 ($2CH_3$); Found (TOF MS EI+) $[M]^+$ 252.1878, $C_{19}H_{24}$ requires 252.1882; NMR data matches literature values.[131]

4'-Methoxy-2,4,6-trimethyl-1,1'-biphenyl (4.3ao)

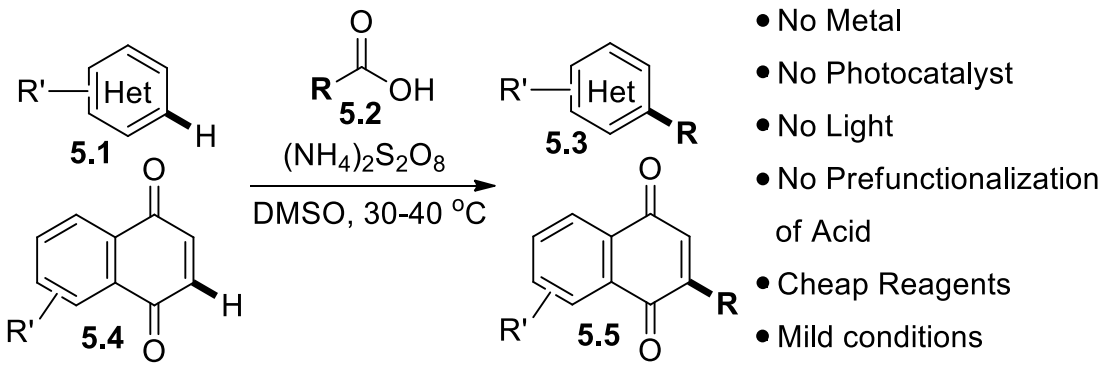


4.3ao

General procedure C followed and crude purified by column chromatography (eluent: 50:1 to 20:1 petrol 40-60 °C/EtOAc) to yield product **4.3ao** as a light yellow oil (6.9 mg (approximately 85% purity), 0.026 mmol, <26%).

R_F 0.26 (20:1 petrol 40-60 °C/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 – 7.09 (2H, m, Ar-H), 6.94 – 6.99 (2H, m, Ar-H), 6.93 (2H, s, Ar-H), 3.86 (3H, s, OCH_3), 2.33 (3H, s, CH_3), 2.01 (6H, s, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2 (C), 138.1 (C), 136.5 (C), 136.3 (2C), 136.1 (C), 129.3 (2CH), 129.2 (2CH), 128.2 (2CH), 21.4 (CH_3), 21.2 (CH_3), 20.9 ($2CH_3$); Found (TOF MS EI+) $[M]^+$ 226.1360, $C_{16}H_{18}O$ requires 226.1358; NMR data matches literature values.[130]

Chapter 5: Metal-, photocatalyst- and light-free, C-H alkylation of *N*-heteroarenes and 1,4-quinones



Acknowledgments

The author would like to thank Conor Oates (MChem project student 2017-2018) for his early optimisation work on this project and Marcos Veguillas for his assistance with the carboxylic acid scope. All work completed by Marcos is clearly marked with Д and all work completed by Conor is clearly marked with Ѫ.

5.1 Introduction

5.1.1 Introduction to the Minisci reaction

N-Heteroarenes and 1,4-quinones are very privileged motifs, being present in a large portion of natural products, pharmaceuticals and ligand scaffolds[132-136] (e.g. Figure 5.1, also see Table 5.7). The importance of these motifs has led to a great deal of research into their late stage modification and in particular C-H functionalisation.[137, 138]

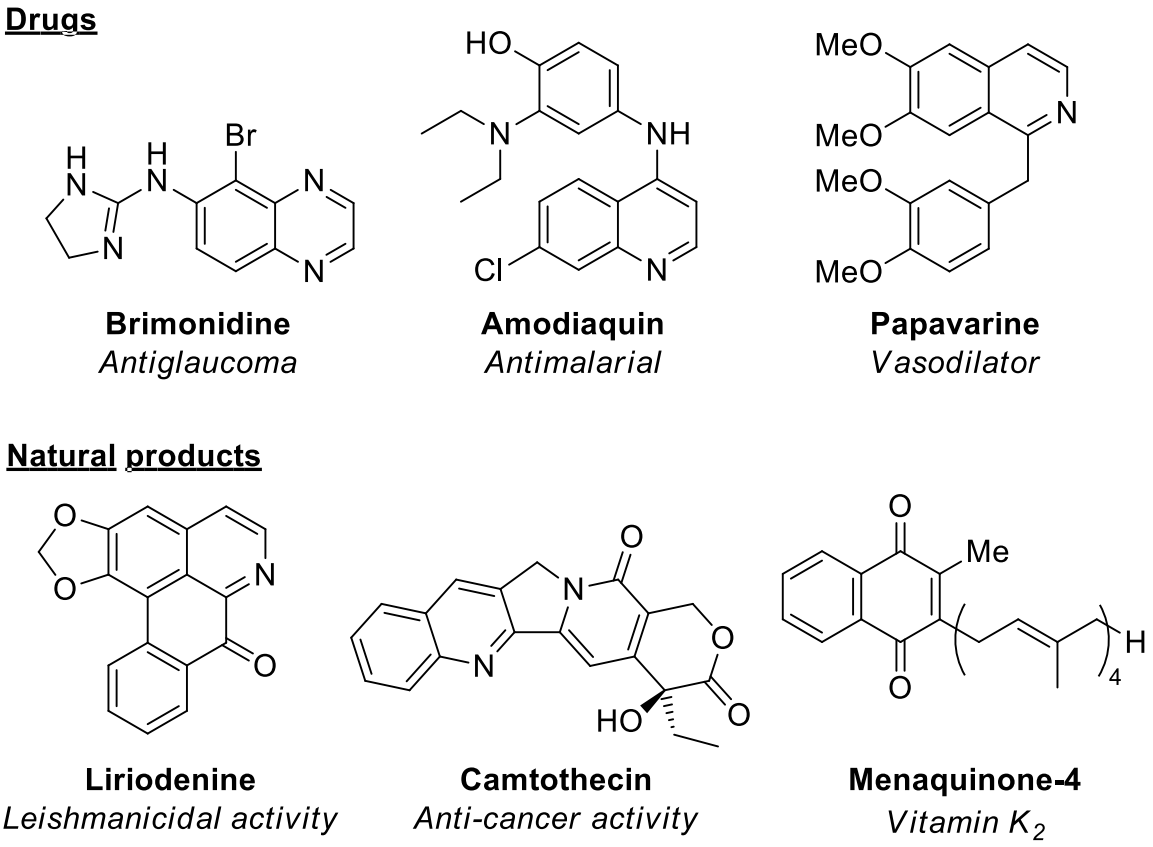
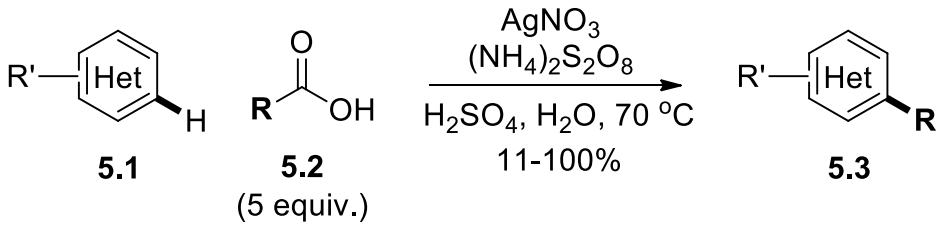
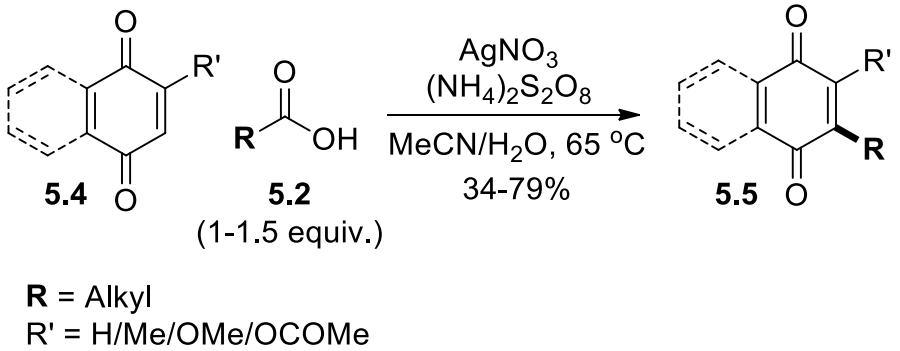


Figure 5.1: Pharmaceuticals and natural products containing *N*-Heteroarenes and 1,4-quinones motifs[133, 136]

Since many *N*-heteroarenes and 1,4-quinones are electron-poor, their functionalisation is dominated by Minisci-type chemistry with many examples of late-stage modifications being carried out in this way.[139] However, the silver-mediated conditions originally developed by Minisci for the alkylation of *N*-heteroarenes[140, 141] (Scheme 5.1) and those reported later for the alkylation of 1,4-quinones[142] (Scheme 5.2) are harsh and have a limited scope, with varying yields.



Scheme 5.1: Silver-mediated alkylation of *N*-Heteroarenes reported by Minisci[140]



Scheme 5.2: Silver-mediated alkylation of 1,4-quinones reported by Jacobsen[142]

$$S_2O_8^{2-} + Ag^+ \longrightarrow SO_4^{\bullet -} + SO_4^{2-} + Ag^{2+}$$

$$Ag^{2+} + RCO_2H \longrightarrow R^{\bullet} + CO_2 + H^+ + Ag^+$$

Scheme 5.3: Proposed mechanism for the generation of the alkyl radical under Minisci's conditions[140]

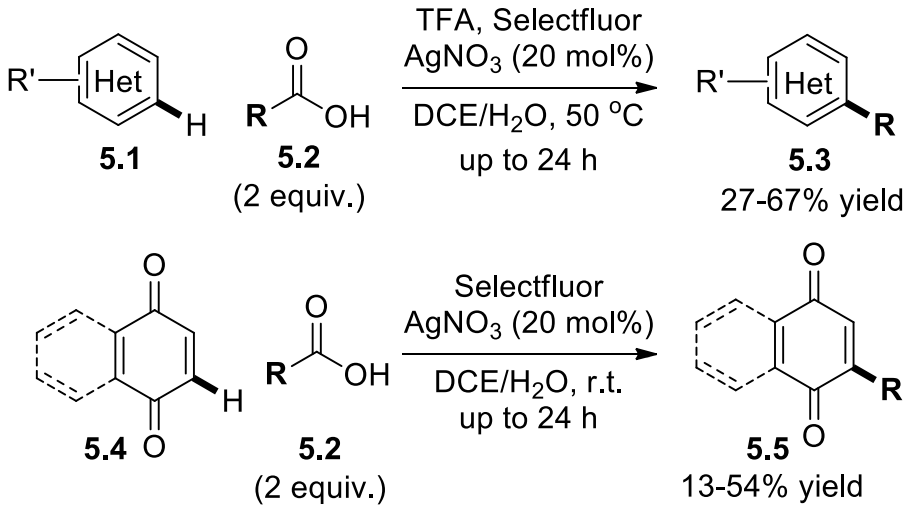
The Minisci reaction is thought to proceed through the oxidation of the Ag^+ by the persulfate oxidant to give Ag^{2+} which can then oxidise the carboxylic acid, regenerating the Ag^+ ion and causing decarboxylation of the carboxylic acid to give the alkyl radical (Scheme 5.3). The alkyl radical can then undergo addition to the protonated *N*-heteroarene or the 1,4-quinone providing the alkylated product after loss of one electron and deprotonation.[140]

Since, the first publications by Minisci[140, 141] and Jacobsen[142] there have been many reports which have endeavoured to make the Minisci reaction milder and more substrate scope tolerant, and thereby more applicable to late-stage C-H functionalisations. Many of these reports use alternative coupling partners to the cheap and readily available carboxylic acids originally used by Minisci (Scheme 5.1).

These alternative radical sources include alkyl halides,[143, 144] boronic acids[145-148] and their derivatives,[149, 150] sulfonates,[151, 152] peroxides[153] and acid chlorides[154] and are used in conjunction with metal- or photoredox-catalysis. However, the focus of this project, and therefore introduction, will be on procedures using carboxylic acids as the radical source and methodologies which are metal- and photocatalyst-free. Carboxylic acids were chosen as the radical source in this project because as well as being cheap and readily available they are also stable, non-toxic, naturally abundant, and release only traceless CO_2 upon breakdown.[155]

5.1.2 Minisci-type reactions using carboxylic acids

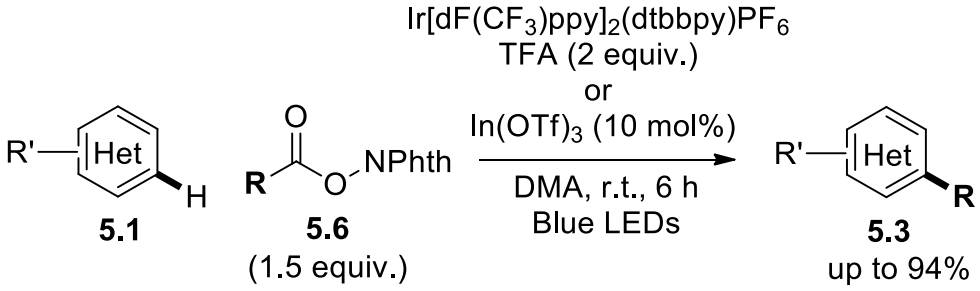
In recent years many novel approaches have been developed to make the Minisci-type alkylation of *N*-heteroarenes and 1,4-quinones more mild and so well-suited to late-stage C-H functionalisations. In 2017, Baxter reported a silver-catalysed Minisci-type procedure for the alkylation of *N*-heteroarenes and 1,4-quinones using selectfluor as an oxidant[148] (Scheme 5.4). A reasonable range of substrates as well as primary, secondary and tertiary carboxylic acids were tolerated in the reaction. However, the yields for the alkylation are moderate and the procedure requires silver as a catalyst in fairly high loading (Scheme 5.4).



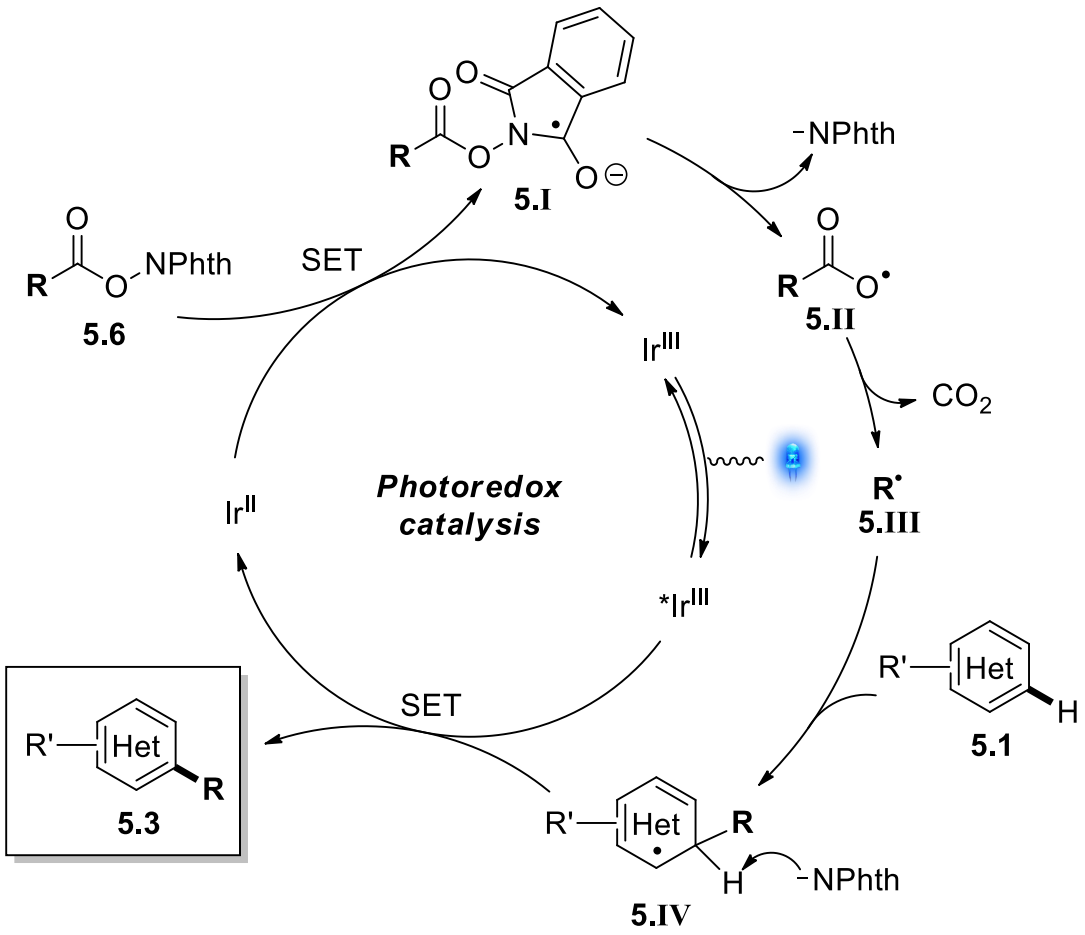
Scheme 5.4: Silver-catalysed alkylation using mild oxidant[148]

The generation of the alkyl radical can instead be achieved through photocatalysis, avoiding the use of silver and rendering the reaction milder. Photocatalysed Minisci-type reactions were first achieved with redox active esters as the radical source[156]

(Scheme 5.5). Reported in 2017, this high yielding procedure is very tolerant of a range of *N*-heteroarenes[156] and can also be used for the coupling of peptides under similar conditions.[157] Additionally, with the addition of a chiral Brønsted acid catalyst, this reaction can be made enantioselective.[158] Although this reaction has excellent applications and is very tolerant and high yielding, the use of a redox active ester rather than the carboxylic acid itself is a major drawback. Although the redox active esters are easily prepared from the carboxylic acid, the extra step needed to prepare the ester is undesirable and makes the reaction very atom inefficient. Dhar recently reported a one-pot version of this reaction[159] which removes the need for the prefunctionalisation step but does not improve the atom-efficiency of the method.



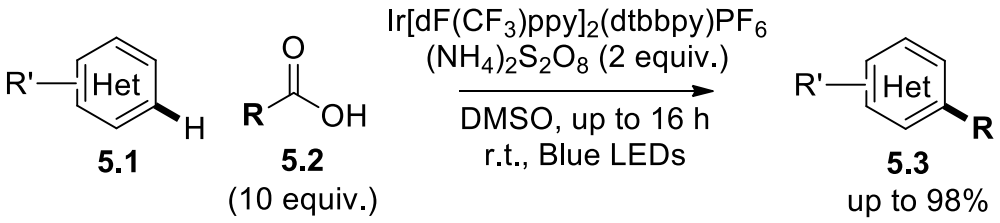
Scheme 5.5: Redox active ester and photocatalysis for the alkylation of *N*-heteroarenes[156]



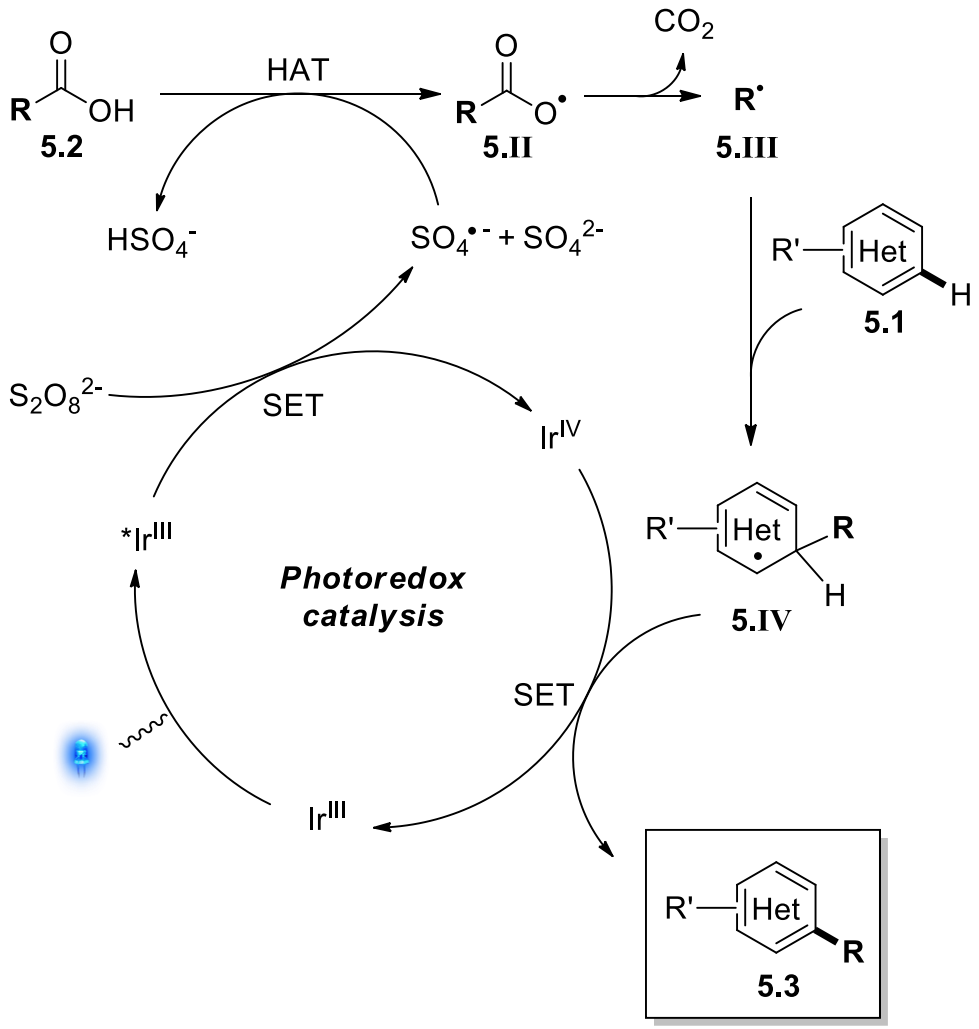
Scheme 5.6: Proposed photocatalytic cycle for the alkylation of *N*-heteroarenes with redox active esters[156]

The mechanism of this reaction proceeds through a single electron transfer (SET) from the Ir^{II} catalyst to the redox active ester **5.6** giving the intermediate **5.I** which breaks down to provide the alkyl radical **5.III**. The product **5.3** is then produced through deprotonation and SET to the excited state iridium photocatalyst to regenerate the active Ir^{II} catalyst.

As discussed, the main drawback of using redox active esters **5.6** is the need to prefunctionalise the carboxylic acid. This can be avoided by using the carboxylic acid directly in a photocatalysed alkylation protocol without the use of a silver catalyst, something first achieved by Glorius in 2017.[160] Glorius's mild, tolerant and high yielding method (Scheme 5.7) is proposed to operate through hydrogen atom transfer (HAT) from the carboxylic acid to the radical sulfate anion (Scheme 5.8).



Scheme 5.7: Photocatalytic procedure for the alkylation of *N*-heteroarenes with carboxylic acids[160]



Scheme 5.8: Proposed photocatalytic cycle for the alkylation of *N*-heteroarenes with carboxylic acids[160]

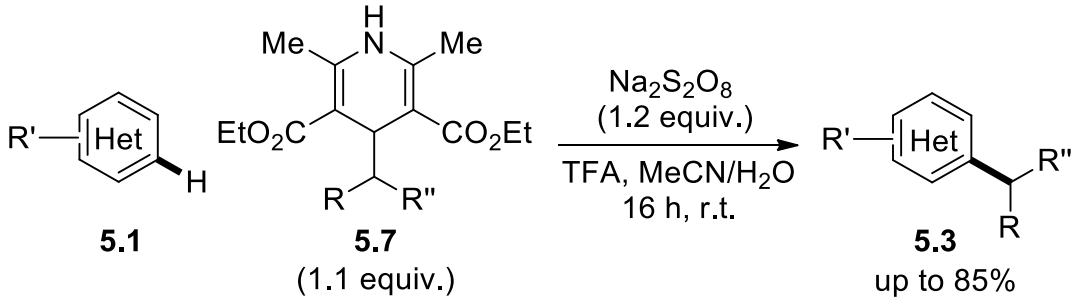
In the mechanism proposed by Glorius, the radical sulfate anion ($SO_4^{\cdot-}$) is generated by the breakdown of the persulfate through SET from the photocatalyst. The radical sulfate anion then abstracts a radical H from the carboxylic acid **5.2**, causing decarboxylation to provide the alkyl radical **5.III**. Radical addition of **5.III** to the *N*-

heteroarene gives the intermediate **5.IV**, which is converted to the product **5.3** through deprotonation and SET to the photocatalyst.

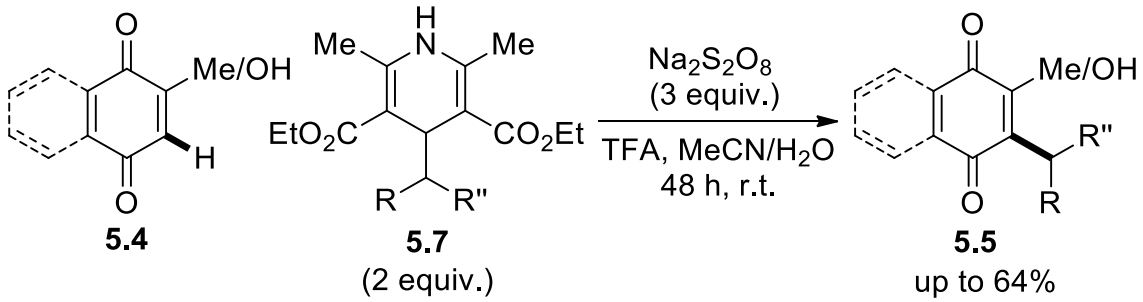
The alkylation of *N*-heteroarenes using carboxylic acids was also achieved independently by the groups of Chen,[161] Zhang[162] and Frenette[163] in 2018. These procedures all employ a combination of hypervalent iodine reagents and either photocatalysis or light to generate the alkyl radical. Importantly, none of the light based procedures described in this section are suited to 1,4-quinones. This is perhaps due to 1,4-quinones being light sensitive and so only suited to light- and photocatalyst-free reactions (see Section 5.3.1).

5.1.3 Metal- light- and photocatalyst-free Minisci-type reactions

Metal- light- and photocatalyst-free Minisci-type alkylations were achieved by Molander[164] in 2017, although not with carboxylic acids as the radical source. Molander and co-workers employed 1,4-dihydropyridines (DHPs) **5.7** in their procedure, achieving good yields for the alkylation of both *N*-heteroarenes (Scheme 5.9) and 1,4-quinones (Scheme 5.10). However, the procedure is limited to mainly secondary alkyl radicals and requires the preparation of the DHPs **5.7** used as substrates.



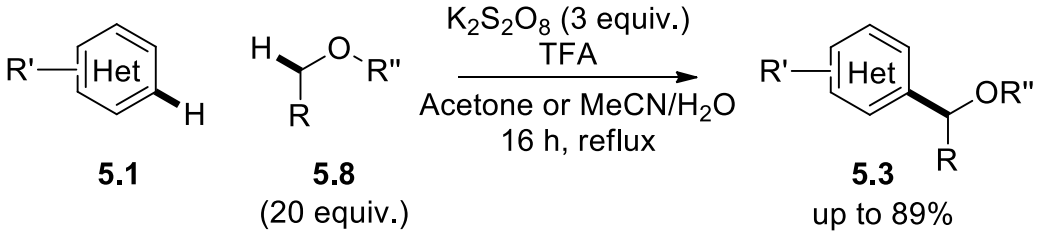
Scheme 5.9: Metal- light- and photocatalyst-free alkylation of *N*-heteroarenes with 1,4-dihydropyridines[164]



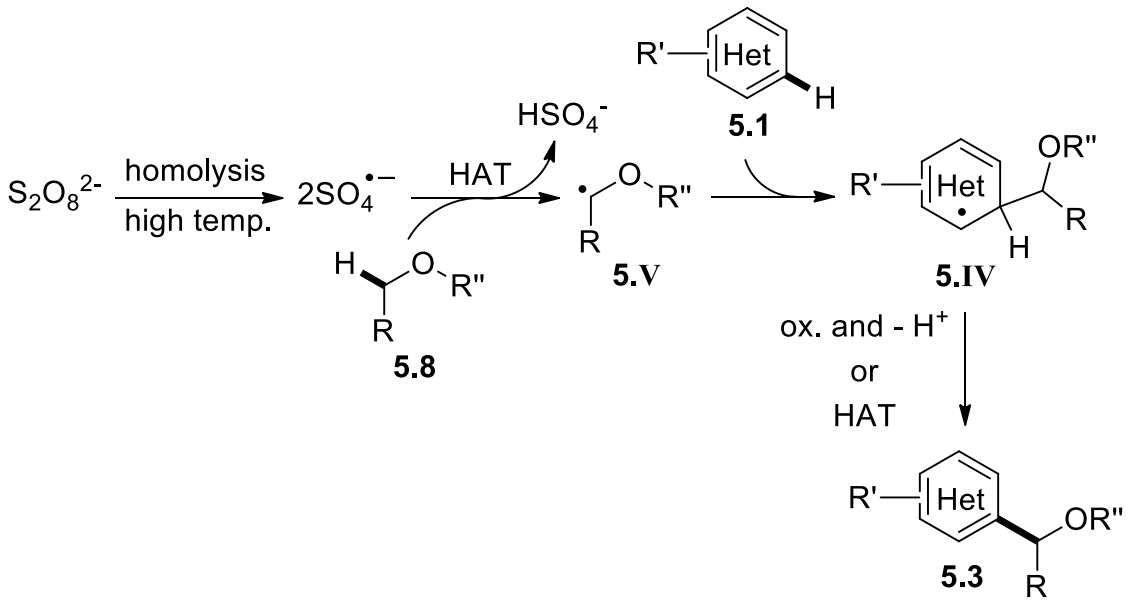
Scheme 5.10: Metal- light- and photocatalyst-free alkylation of 1,4-quinones with 1,4-dihydropyridines[164]

Under the reaction conditions developed by Molander and co-workers, the DHP is thought to be readily oxidised to generate the alkyl radical without the need for a metal catalyst or light irradiation. Although this allows for a large scope of *N*-heteroarenes and 1,4-quinones, the need to synthesise the alkyl radical source from the corresponding aldehydes is a main drawback to this procedure. A methodology allowing the direct use of a cheap and commercially available alkyl radical source would be much more desirable. Interestingly, the alkylation of *N*-heteroarenes with unactivated ethers has been shown to be possible under metal- light- and photocatalyst-free conditions.

The alkylation of *N*-heteroarenes with unactivated ethers was originally reported by MacMillan under photoredox conditions[165] but the reaction was later found to be possible without the use of a photocatalyst[166] and then, later again, under photocatalyst- and light-free conditions[167] albeit at much higher temperatures (Scheme 5.11).



Scheme 5.11: Metal- light- and photocatalyst-free alkylation of *N*-heteroarenes with unactivated ethers[167]

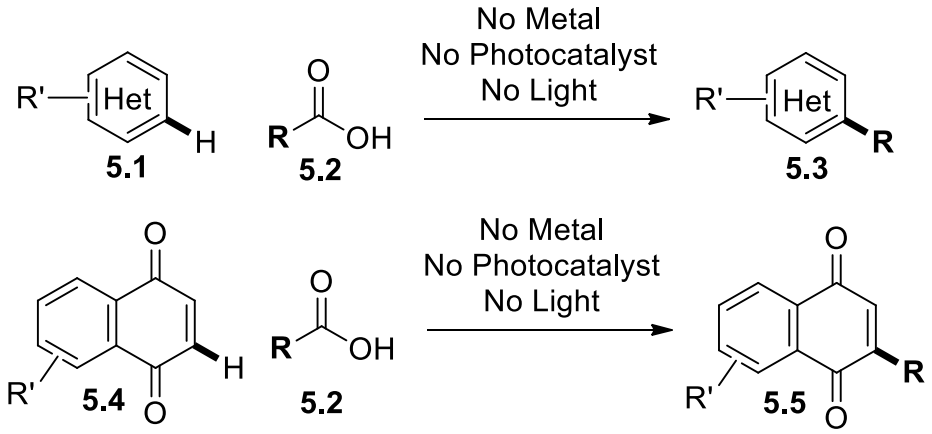


Scheme 5.12: Proposed mechanism for the alkylation of *N*-heteroarenes with unactivated ethers[167]

The metal-, light- and photocatalyst-free alkylation of *N*-heteroarenes with unactivated ethers, reported by Barriault, is thought to proceed through the generation of the alkyl radical by hydrogen atom transfer (HAT).[167] The radical H is abstracted from the unactivated ether **5.8** by the radical sulfate anion which is generated by homolysis of the persulfate. The generation of the radical sulfate anion by homolysis of the persulfate rather than under photocatalytic conditions is key to this procedure (Scheme 5.12). This is particularly interesting if the radical sulfate anion can be produced under photocatalyst- and light-free conditions and, as reported by Glorius, the radical sulfate anion can produce alkyl radicals through HAT of carboxylic acids, then metal-, light- and photocatalyst-free Minisci-type alkylations with carboxylic acids may be possible.

5.2 Project aims

The aim of the project was to develop the first mild, metal-, light- and photocatalyst free Minisci-type alkylation procedure which uses cheap and readily available carboxylic acids and is suitable for the late-stage C-H functionalisation of *N*-heteroarene and 1,4-quinone moieties.

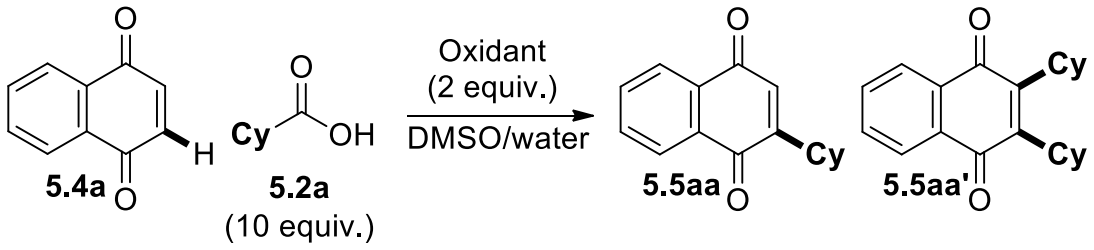


Scheme 5.13: Desired metal- light- and photocatalyst-free alkylation of *N*-heteroarenes and 1,4-quinones with carboxylic acids

In recent years, there have been many publications describing milder (<50 °C), Minisci-type alkylation procedures which are better suited to the late-stage C-H alkylation of *N*-heteroarene and 1,4-quinone moieties. Since these moieties are very prevalent in nature and present in a large number of medicinally relevant compounds, their mild late-stage C-H alkylation is highly sought after.[132-136] However, as discussed in section 5.1, many of the recent publications in this area use metal, light and photocatalysis to achieve alkylation with carboxylic acids.[148, 156-163] Additionally, reports which are metal-, light- and photocatalyst-free require the use of an alternative alkylating agent which must be prepared prior to the alkylation.[164] The development of a procedure which uses readily available carboxylic acids without the need for metal, light or photocatalysis would be a significant advance in the field because the methodology would not require expensive photocatalysts or additives, would use cheap starting materials without prefunctionalisation and would also be tolerant to light-sensitive substrates which degrade under photocatalytic conditions.

5.3 Results and discussion

5.3.1 Optimisation



Entry	Conc. (mol/L)	DMSO: H_2O Ratio*	Temp. (°C)	Time (h)	Oxidant	LEDs	SM **5.4** (%)	Ratio **5.5**:**5.5'**	Yield **5.5** (%)[a]
1[b]	1	1:0	r.t	16	$(NH_4)_2S_2O_8$	Blue	7	>20:1	9
2[X]	1	1:0	30	16	$(NH_4)_2S_2O_8$	Blue	22	>20:1	16
3[c][X]	1	1:0	30	16	$(NH_4)_2S_2O_8$	Blue	28	-	-
4[c][X]	1	1:0	30	72	$(NH_4)_2S_2O_8$	Green	87	-	-
5	1.33	600:1	30	40	$(NH_4)_2S_2O_8$	Green	26	>20:1	53
6	2	600:1	30	40	$(NH_4)_2S_2O_8$	Green	21	>20:1	59
7	2	30:1	30	40	$(NH_4)_2S_2O_8$	Green	21	>20:1	60
8[d]	2	600:1	30	40	$(NH_4)_2S_2O_8$	Green	43	>20:1	31
9[X]	2	600:1	30	40	$Na_2S_2O_8$	Green	30	>20:1	45
10[X]	2	600:1	30	40	$K_2S_2O_8$	Green	80	>20:1	9
11[X]	2	600:1	30	40	*t*-Bu_2O_2	Green	86	-	0
12[X]	2	600:1	30	40	DDQ	Green	85	-	0
13[X]	2	600:1	30	40	-	Green	83	-	0
14	2	600:1	30	66	$(NH_4)_2S_2O_8$	Green	9	8:1	64
15[e]	2	600:1	30	40	$(NH_4)_2S_2O_8$	Green	15	11:1	56
16[f]	2	600:1	30	40	$(NH_4)_2S_2O_8$	Green	<5	8:1	68
17	2	600:1	40	40	$(NH_4)_2S_2O_8$	Green	<5	1.7:1	54
18	2	600:1	40	16	$(NH_4)_2S_2O_8$	Green	<5	>20:1	70
19[g]	2	600:1	40	16	$(NH_4)_2S_2O_8$	-	<5	>20:1	71
20[h][X]	2	600:1	40	16	$(NH_4)_2S_2O_8$	-	<5	>20:1	54
21[i][X]	2	600:1	40	16	$(NH_4)_2S_2O_8$	-	16	>20:1	54

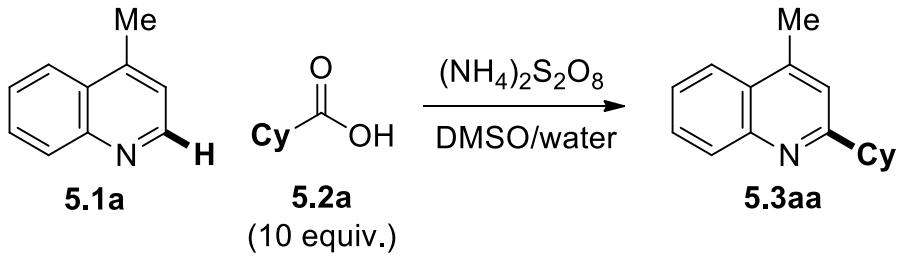
[a]Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard, [b] $[Ir(dF(CF_3)ppy)dtbbpy)]PF_6$ (2 mol%), [c] Control - No acid **5.2a** added, [d] Reaction carried out under air, [e] 20 equiv. $CyCO_2H$ **5.2a**, [f] 4 equiv. oxidant [g] Reaction carried out in dark: Schlenk flask wrapped thoroughly with aluminium foil and reproduced 3 times, [h] 5 equiv. $CyCO_2H$ **5.2a**, [i] 1 equiv. oxidant. *During our studies, yields were found to be approximately 10% better in "wet" solvent than anhydrous DMSO, so the 600:1 DMSO:H_2O ratio was adopted to obtain consistency in yields.

Table 5.1: Optimisation of the monoalkylation of 1,4-naphthoquinone

The initial aim of this project was to develop suitable photoredox conditions to allow the alkylation of 1,4-quinones. Inspired by Glorius's work on the alkylation of

N-heteroarenes (Scheme 5.7), we first subjected 1,4-naphthoquinone to Glorius's conditions (Entry 1, Table 5.1). Glorius's conditions (Entry 1, Table 5.1) gave only traces of our desired product despite almost all of the starting material **5.4a** being consumed. A control reaction without photocatalyst (Entry 2, Table 5.1) showed that the small amount of product we were seeing was due to the uncatalysed background reaction and the degradation of the starting material **5.4a** was still occurring. Further control reactions (Entry 3, Table 5.1) showed that the 1,4-naphthoquinone **5.4a** is unstable under blue LED irradiation, but to our delight, is more stable under green LED irradiation (Entry 4, Table 5.1). Inspired by the work of Shah[166] we then attempted the reaction without any photocatalyst and obtained a pleasing yield of 53% under the green LED only conditions (Entry 5, Table 5.1). Increasing the dilution slightly gave a cleaner reaction with a marginally better yield (59%, Entry 6, Table 5.1). Increasing the equivalents of water had no effect on the yield (60%, Entry 7, Table 5.1) but as expected the yield was lower when the reaction was carried out under air (31%, Entry 8, Table 5.1). We then looked to screen a range of different oxidants only to find that our initial choice of oxidant (59%, Entry 6, Table 5.1) outperformed the others trialled (45% and 9%, Entries 9 and 10, Table 5.1) and that the persulfate was crucial for the reaction to occur (Entries 10-13, Table 5.1). In an attempt to obtain full conversion of the starting material and improve the yield, we then increased the reaction time, equivalents of carboxylic acid and equivalents of oxidant (Entries 14, 15 and 16 respectively, Table 5.1). All of these changes to the conditions gave an increase in the conversion of starting material. However, increasing the temperature slightly to 40 ^{o}C (Entry 17, Table 5.1) was deemed the most atom efficient and synthetically useful change. Reducing the reaction time to 16 h provided excellent selectivity for the mono-alkylated product **5.5aa** over the dialkylation product **5.5aa'** and provided our optimised conditions (70%, Entry 18, Table 5.1). To our surprise, when we conducted a control reaction omitting all light from the reaction we obtained exactly the same yield (71%, Entry 19, Table 5.1). Unfortunately, attempts to reduce the equivalents of oxidant or carboxylic acid had an adverse effect on the yield (Entries 20 and 21, Table 5.1) but this result (Entry 19, Table 5.1) shows that as well as not requiring a metal or photocatalyst our newly optimised conditions also do not require light. Realising the potential value of a metal- light- and photocatalyst-free alkylation procedure which

was applicable to both 1,4-quinones and *N*-heteroarenes, we next investigated the alkylation of lepidine **5.1a**.



Entry	Conc. (mol/L)	DMSO: H_2O ratio	Temp. (°C)	Time (h)	Oxidant (equiv.)	[Ir] (mol%)	Equiv. **5.2a**	SM **5.1a** (%)	Yield **5.3aa** (%)
1[a],[b]	*1*	-	*r.t.*	*1.5*	*2*	*0.5*	*10*	*NR*	*94(81)*
2[a]	*1*	-	*r.t.*	*1.5*	*2*	*0.5*	*10*	*NR*	*8*
3[c]	1	-	r.t.	16	2	0.5	10	89	9
4[c]	0.5	600:1	40	16	2	-	10	15	69
5[c]	0.5	600:1	40	16	3	-	10	<5	79(82)
6[c]	0.5	600:1	40	16	3	0.5	10	20	76
7[c]	0.5	600:1	40	16	3	-	5	41	54
8[c],[d]	0.5	600:1	40	16	3	-	5	56	43

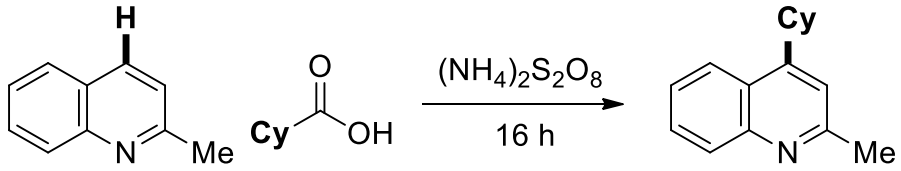
[a] Conditions reported by Glorius and coworkers[168], ^{1}H NMR yields (isolated yield). [b] Blue LED irradiation. [c] Yields determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard, [d] TFA (1.5 equiv.) added. [Ir] = [Ir(dF(CF_3)ppy)dtbbpy)]PF_6, *NR* – Not reported

Table 5.2: Investigation into the alkylation of lepidine **5.1a**

To our delight, the alkylation of lepidine **5.1a** under our new conditions gave the desired product in good NMR yield (69%, Entry 4, Table 5.2). Since Glorius had achieved the alkylation of *N*-heteroarenes under photocatalytic conditions we looked to investigate the difference between the two procedures. Under blue light irradiation Glorius reports an excellent yield of **5.3aa** in just 1.5 h (81%, Entry 1, Table 5.2) and very low NMR yield without irradiation (8%, Entry 2, Table 5.2). Suspecting that under longer reaction times the control reaction reported by Glorius (Entry 2, Table 5.2) may give a higher yield through a non-photocatalytic pathway, a control reaction under the same condition was allowed to react for 16 h (Entry 3, Table 5.2). There was, however, no increase in yield due to the longer reaction time (8% *vs.* 9%, Entry 2 *vs.* Entry 3, Table 5.2) suggesting that the slightly increased temperature and dilution is crucial for the non-photocatalytic conditions to be high-yielding. It was later shown that the

inclusion of the iridium photocatalyst is slightly detrimental to the non-photocatalytic conditions (Entry 6, Table 5.2). Pleasingly, the initial conditions trialled for the alkylation of lepidine **5.1a** (69%, Entry 4, Table 5.2) could be optimised further for *N*-heteroarenes simply by increasing the equivalents of oxidant (82%, Entry 5, Table 5.2). Reducing the equivalents of carboxylic acid **5.2a** was found to be detrimental to the reaction (54%, Entry 7, Table 5.2) and could not be improved with the inclusion of 1.5 equiv. of TFA to activate the heterocycle (43%, Entry 7, Table 5.2).

A final investigation into the conditions was carried out with the substrate **5.1b** (Table 5.3). This solvent study showed that DMSO was the only solvent which facilitated the reaction (Entries 2-7 *vs.* Entry 1, Table 5.3). It should be noted that no product is observed when acetonitrile and/or water, common solvents for the Minisci reaction, is employed (Entries 2-4, Table 5.3). Pleasingly, the reaction was found to occur at the even milder temperature of 30 °C but complete conversion of the starting material was not observed after 16 h (Entry 8, Table 5.3).



5.1b **5.2a** (10 equiv.) **5.3ba**

Entry	Conc. (mol/L)	Solvent	Solvent ratio	Temp. (°C)	Oxidant (equiv.)	SM **5.1b** (%)	Yield **5.3ba** (%)[a]
1	0.5	DMSO/H_2O	600:1	40	3	<5	91(80)
2	0.5	H_2O	-	40	3	80	0
3	0.5	H_2O/MeCN	2:1	40	3	90	0
4	0.5	MeCN	-	40	3	90	0
5	0.5	Acetone	-	40	3	94	0
6	0.5	DMF	-	40	3	-	0
7	0.5	MeOH	-	40	3	85	0
8	0.5	DMSO/H_2O	600:1	30	3	19	73

[a] Yields determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard (isolated yield)

Table 5.3: Investigation into the alkylation of quinaldine **5.1b**

It is thought that DMSO is crucial for the metal-, light- and photocatalyst-free reaction as it improves the rate at which homolysis of the persulfate occurs. The rate at which persulfate is broken down under thermal conditions is reported to be very solvent dependent[169] and DMSO can increase the rate of homolysis significantly.[170] The homolysis of persulfate is proposed to be central to the mechanism (see Section 5.3.7) and can only occur under these very mild conditions due to the use of DMSO as a solvent. In order to check whether the breakdown of the persulfate could be caused by reaction with DMSO, $(NH_4)_2S_2O_8$ was heated to 40 °C in *d*-DMSO and the solution analysed by ^{1}H NMR. No NMR evidence for the formation of DMSO based intermediates or products were found under our reaction conditions (Figure 5.2 *vs.* Figure 5.3).

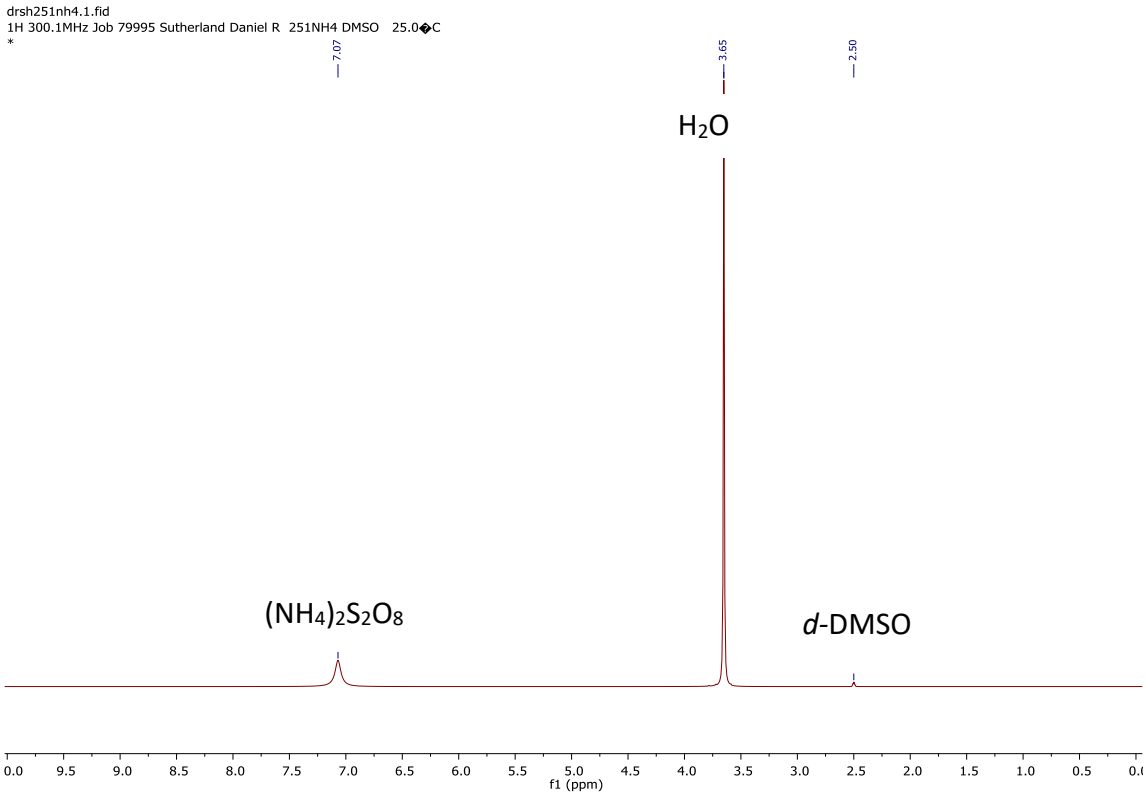


Figure 5.2: ^{1}H NMR of $(NH_4)_2S_2O_8$ in *d*-DMSO under normal conditions

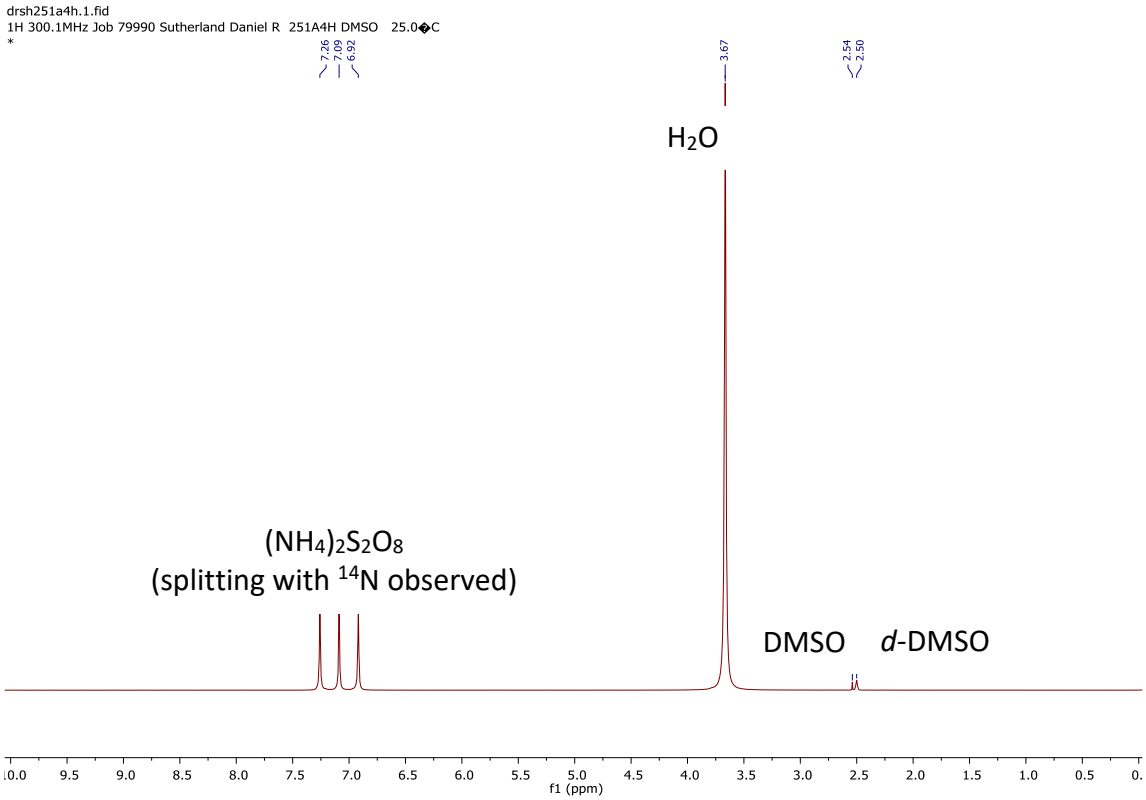
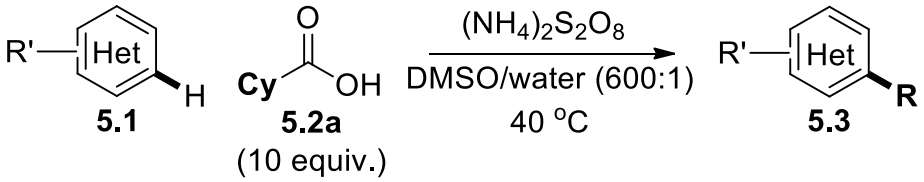
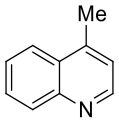
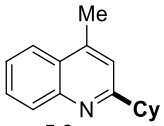
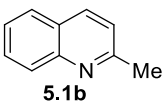
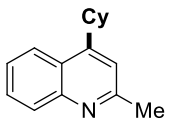
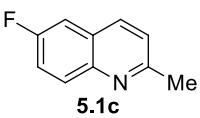
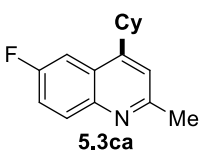
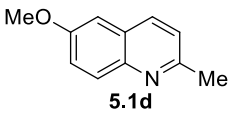
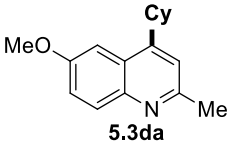
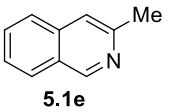
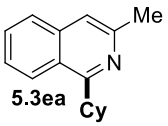
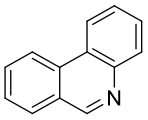
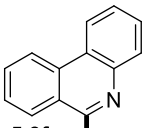
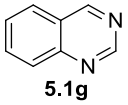
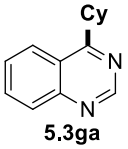
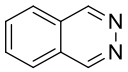
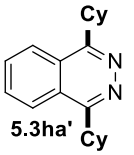
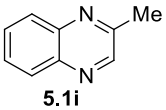
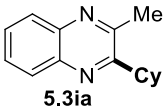
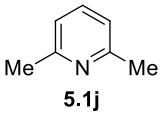
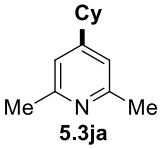
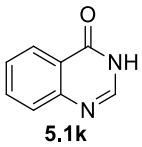
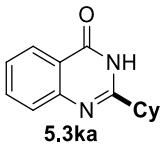
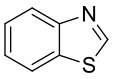
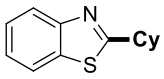


Figure 5.3: ^{1}H NMR of $(NH_4)_2S_2O_8$ in *d*-DMSO after heating at 40 °C for 4 h under N_2

5.3.2 *N*-Heteroarene scope



Entry	*N*-Heteroarene	$(NH_4)_2S_2O_8$ (equiv.)	Time (h)	Major product	Yield[a]
1	 **5.1a**	3	16	 **5.3aa**	82%
2	 **5.1b**	3	16	 **5.3ba**	80%
3	 **5.1c**	3	16	 **5.3ca**	62%

4	 **5.1d**	3	16	 **5.3da**	68%
5	 **5.1e**	3	16	 **5.3ea**	91%
6	 **5.1f**	3	16	 **5.3fa**	80%
7	 **5.1g**	3	16	 **5.3ga**	77%
8[b]	 **5.1h**	6	16	 **5.3ha'**	74%
9	 **5.1i**	4	16	 **5.3ia**	69%
10	 **5.1j**	3	16	 **5.3ja**	50%
11	 **5.1k**	6	24	 **5.3ka**	60%
12	 **5.1l**	6	40	 **5.3la**	25%

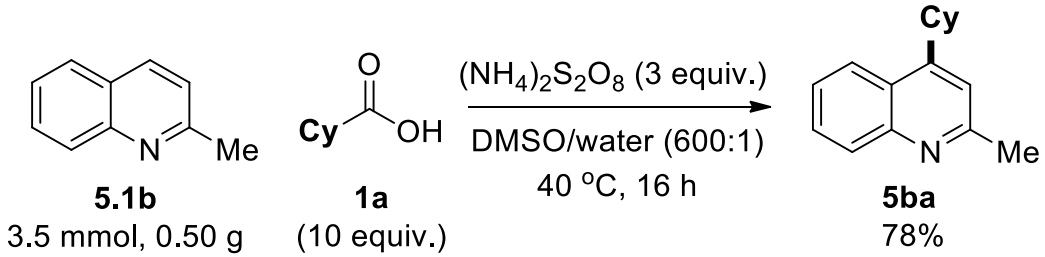
[a] Isolated yields, [b] A 5 : 1 : 1.9 ratio of **5.3ha'**/**5.3ha**/**5.1h** was obtained with 3 equiv. of oxidant.

Table 5.4: *N*-Heteroarene scope

The *N*-heteroarene substrate scope was investigated next and substituted quinolines were investigated first with lepidine **5.1a** and quinaldine **5.1b** giving excellent yields under our conditions (**5.3aa** 82% and **5.3ba** 80%, Entries 1 and 2, Table 5.4). Methoxy- and fluoro- substituted quinaldine were also successfully alkylated in good yields

(**5.3ca** 62% and **5.3da** 68%, Entries 3 and 4, Table 5.4) and **5.3ea** and **5.3fa** were prepared in excellent yields from 3-methylisoquinoline **5.1e** and phenanthridine **5.3f** (91% and 80% respectively, Entries 5 and 6, Table 5.4). Expanding the scope to heteroarenes containing two nitrogen atoms, quinazoline **5.1g** was subjected to the reaction giving **5.3ga** in a pleasing 77% yield (Entry 7, Table 5.4). Under our initial reaction conditions, phthalazine **5.1h** gave a mixture of mono and dialkylated products (5 : 1 : 1.9 ratio of **5.3ha'**/**5.3ha**/**5.1h**). However, to our delight, simply by increasing the equivalents of oxidant, the reaction was successfully adapted to give only the dialkylated product **5.3ha'** (74%, Entry 8, Table 5.3). 2-Methylquinoxaline, 2,6-lutidine and 4(*1H*)-quinazolinone all performed well under our conditions to give the alkylated products **5.3ia**, **5.3ja** and **5.3ka** respectively (69%, 50% and 60%, Entries 9, 10 and 11, Table 5.4). However, the alkylation of the less reactive benzothiazole did not proceed with as high a yield, giving only 25% of product **5.3la** (Entry 12, Table 5.4).

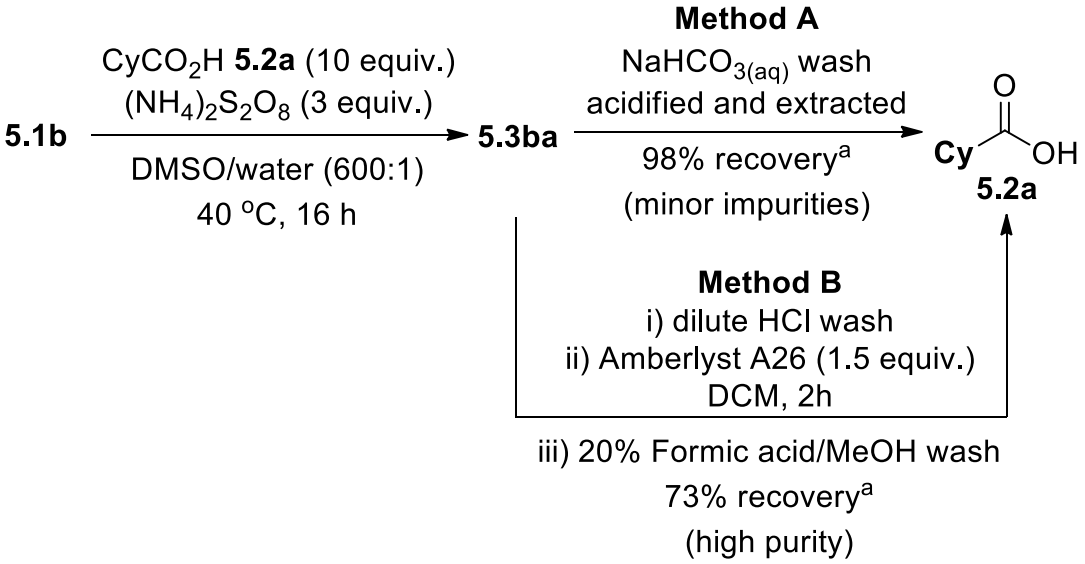
Pleased with our alkylation conditions, we next looked to overcome some of the potential limitations of the procedure. Firstly, the reaction was carried out on an increased scale to investigate whether further scale up in an industrial setting could be possible. To our delight, upon scale up the yield of the reaction remained high (78%, Scheme 5.14 *vs.* 80% on 0.15 mmol scale).



Scheme 5.14: Larger 3.5 mmol scale alkylation of quinaldine **5.1b**[Д]

Another potential drawback of this procedure is the requirement for 10 equivalents of the carboxylic acid. Unfortunately, reducing the equivalents of carboxylic acid resulted in a considerable drop in yield (See Tables 5.1 and 5.2), so we looked to recover the carboxylic acid after the reaction. Pleasingly, almost all of the carboxylic acid can be recovered by aqueous washing, albeit with some minor impurities (98% recovery, Method A, Scheme 5.15, Figure 5.4). Alternatively, the carboxylic acid can be

recovered using a “catch-and release” protocol by utilising Amberlyst A26 to sequester the unreacted carboxylic acid, followed by washing with formic acid/MeOH to release the carboxylic acid into solution. This protocol gives very high purity carboxylic acid in a slightly lower yield of recovery (73% recovery, Method B, Scheme 5.15, Figure 5.5).



[a]NMR yields based on potential recovery of 9 equiv.

Scheme 5.15: Recovery of carboxylic acid

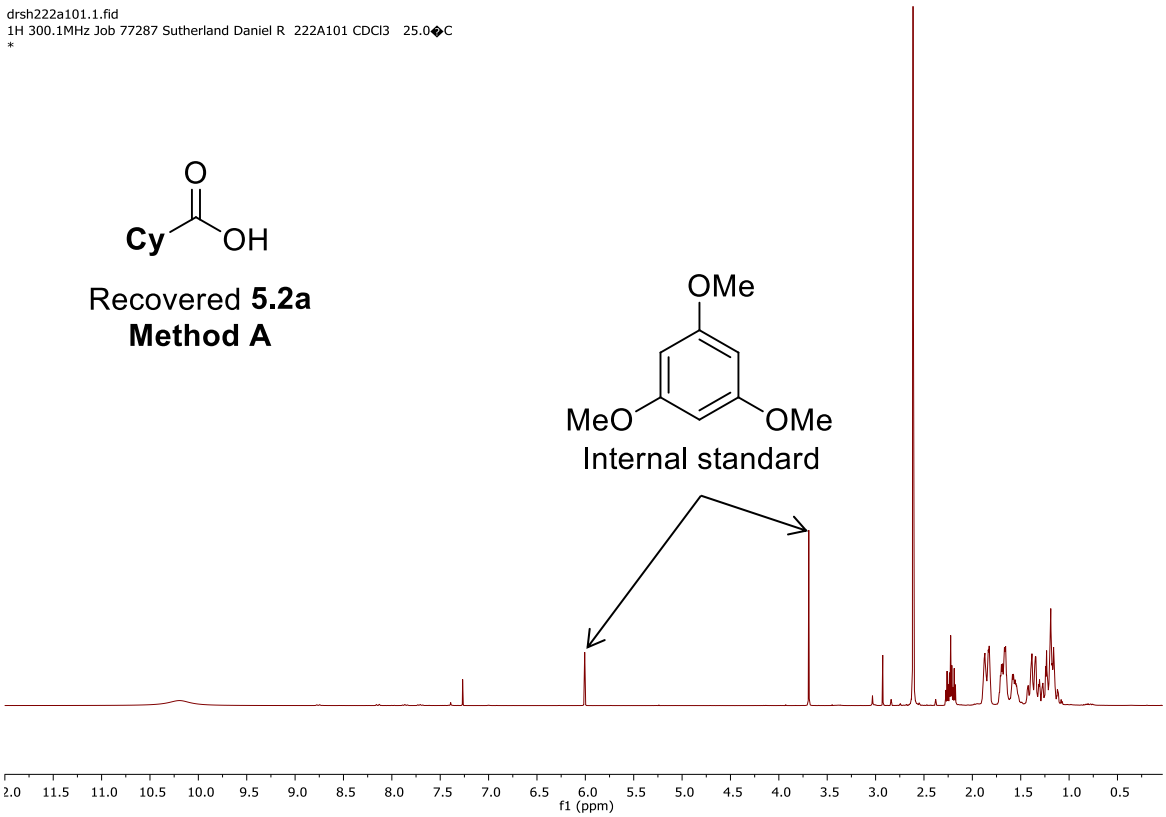


Figure 5.4: Carboxylic acid recovered by aqueous washing

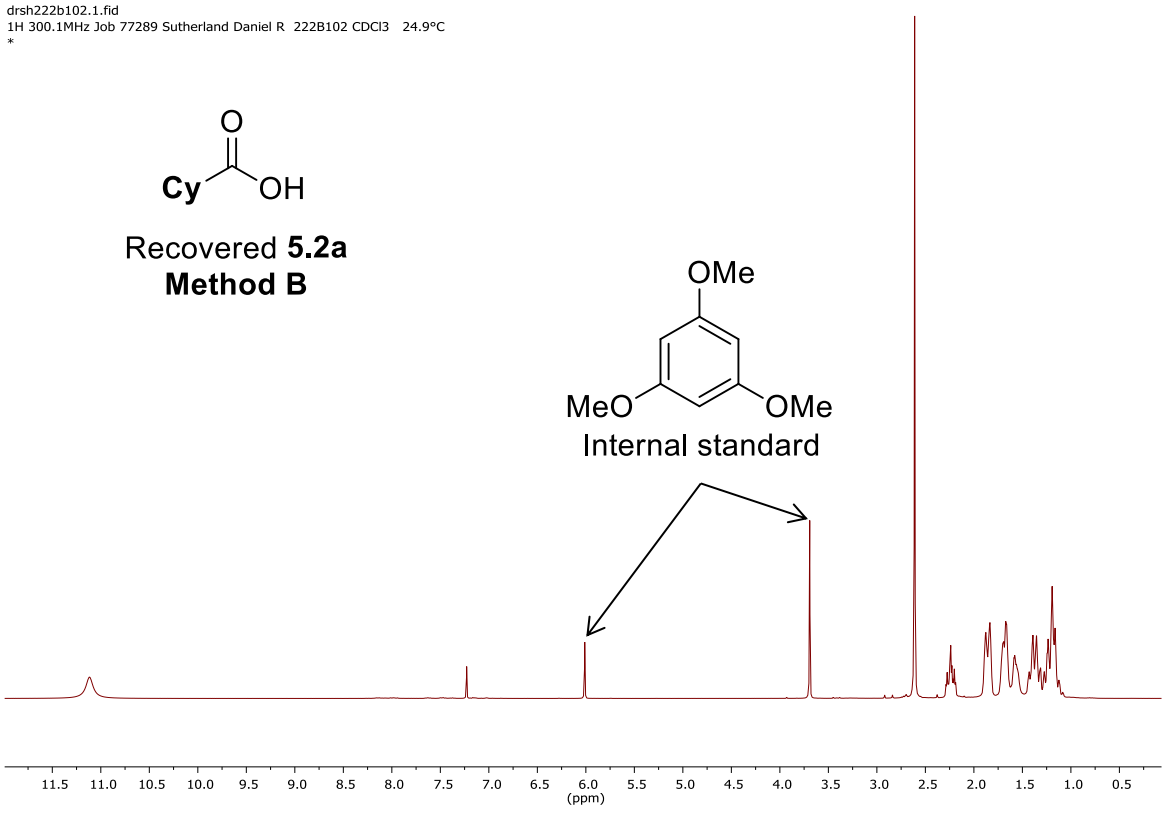
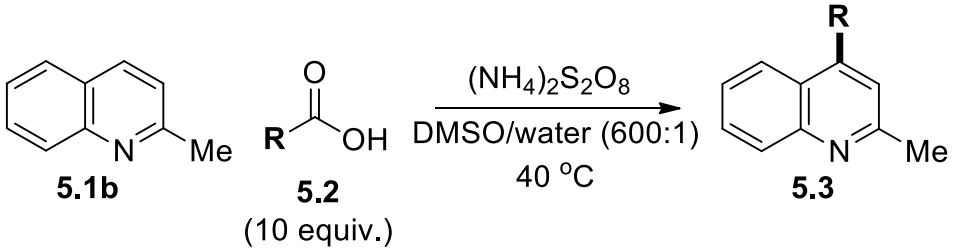
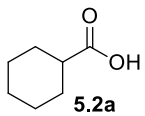
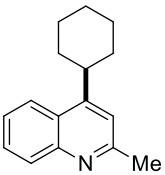
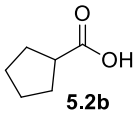
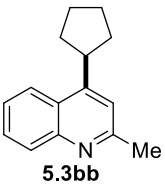
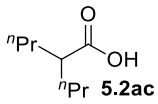
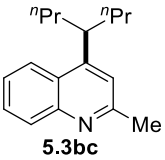
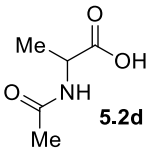
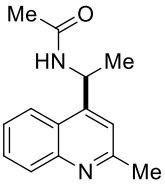
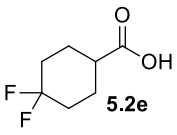
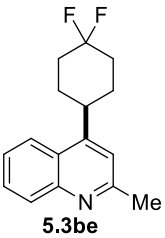
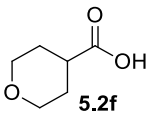
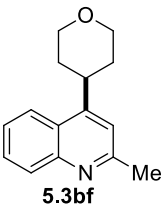
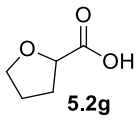
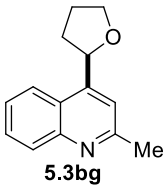
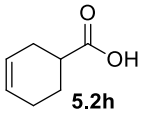
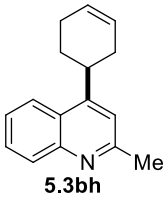
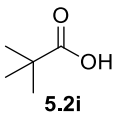
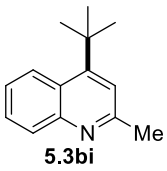
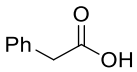
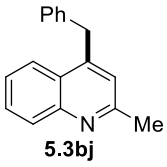
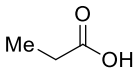
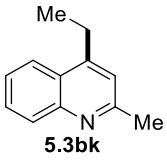
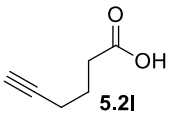
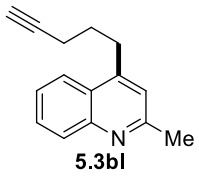
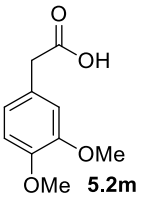
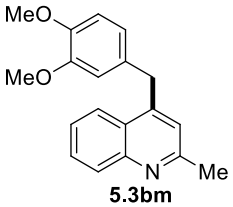
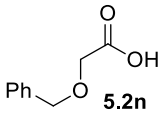
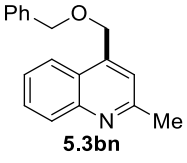


Figure 5.5: Carboxylic acid recovered by "catch-and release" protocol

5.3.3 Carboxylic acid scope



Entry	Carboxylic acid	$(NH_4)_2S_2O_8$ (equiv.)	Time (h)	Major product	Yield[a]
1	 5.2a	3	16	 5.3ba	80%
2[Д]	 5.2b	3	16	 5.3bb	71%
3[Д]	 5.2ac	3	16	 5.3bc	71%
4	 5.2d	3	16	 5.3bd	91%
5[Д]	 5.2e	3	16	 5.3be	74%
6[Д]	 5.2f	3	16	 5.3bf	53%

7[Д]	 **5.2g**	3	16	 **5.3bg**	67%
8[Д]	 **5.2h**	3	16	 **5.3bh**	26%
9[Д]	 **5.2i**	3	16	 **5.3bi**	61%
10[Д]	 **5.2j**	4	16	 **5.3bj**	28%
11[Д]	 **5.2k**	4	16	 **5.3bk**	37%
12[Д]	 **5.2l**	6	72	 **5.3bl**	34%
13	 **5.2m**	6	16	 **5.3bm**	53%
14[Д]	 **5.2n**	3	16	 **5.3bn**	68%

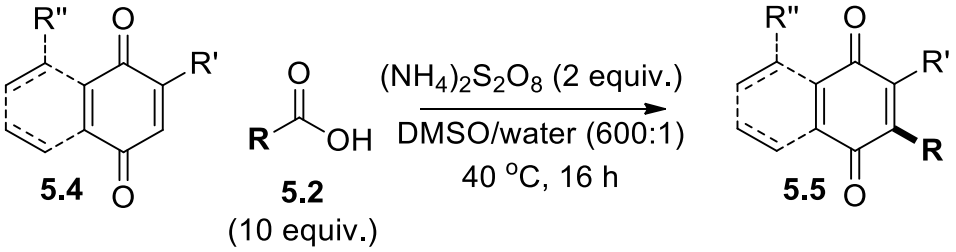
[a] Isolated yields

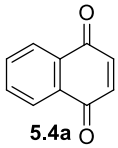
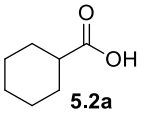
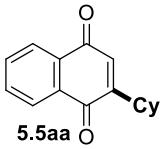
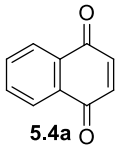
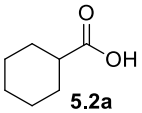
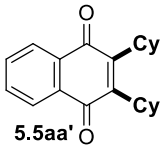
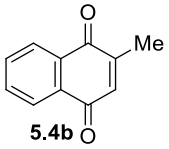
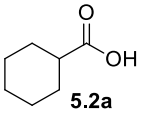
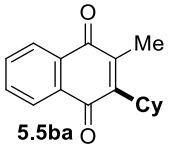
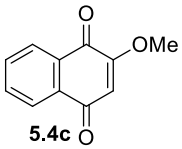
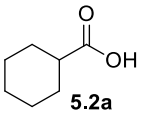
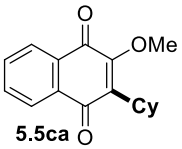
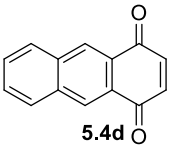
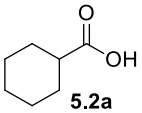
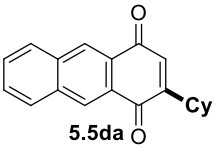
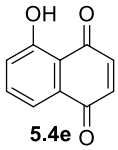
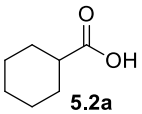
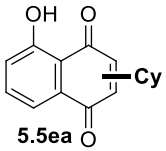
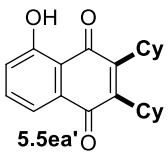
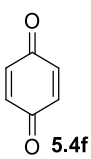
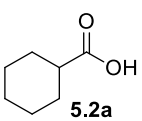
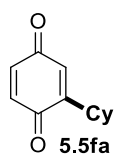
Table 5.5: Carboxylic acid scope

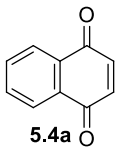
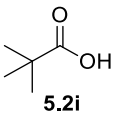
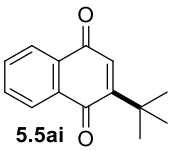
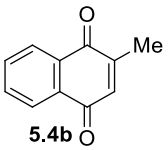
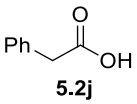
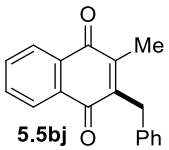
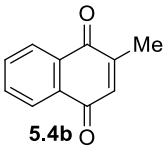
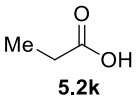
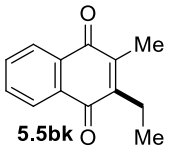
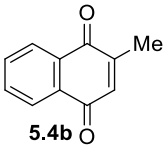
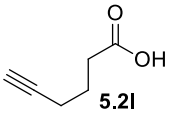
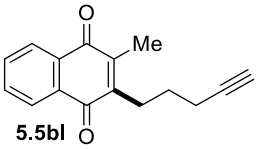
In addition to cyclohexanecarboxylic acid **5.2a** (80%, Entry 1, Table 5.5) a range of other secondary carboxylic acids were tolerated in the reaction with quinaldine **5.1b**,

including other cyclic carboxylic acids (**5.3bb**, 71%, Entry 2, Table 5.5) and straight chain acids (**5.3bc**, 71%, Entry 3, Table 5.5). To our delight, protected amino acid **5.2d** reacted very cleanly to give a yield of 91% (**5.3bd**, Entry 4, Table 5.5) and the fluorinated cyclohexyl carboxylic acid **5.2e** also reacted well (**5.3be**, 74%, Entry 5, Table 5.5). Oxygen containing carboxylic acids were also tolerated well (**5.3bf**, 53%, Entry 6, Table 5.5) even when the heteroatom is directly adjacent to the site of reaction (**5.3bg**, 67%, Entry 7, Table 5.5). Unfortunately, alkenes are not tolerated as well under these conditions with product **5.3bh** being obtained in only 26% yield (Entry 8, Table 5.5). Alkylation with the tertiary carboxylic acid, pivalic acid, did proceed well however giving a 61% yield of **5.3bi** (Entry 9, Table 5.5). Primary carboxylic acids initially seemed less suited to the reaction conditions (**5.3bj** 28% and **5.3bk** 37%, Entries 10 and 11, Table 5.5) but later showed good yields when coupled with menadione **5.4b** (see Table 5.6). Pleasingly, the formation of product **5.3bl** (34%, Entry 12, Table 5.5) shows that the alkyne moiety is tolerated in the reaction and the yield with primary carboxylic acids can be greatly improved by using a more electron-rich benzyl carboxylic acid (**5.3bm**, 53%, Entry 13, Table 5.5) or by having an oxygen adjacent to the reaction site (**5.3bn**, 68%, Entry 14, Table 5.5).

5.3.4 Alkylation of 1,4-quinone scope



Entry	*N*-Heteroarene	Carboxylic acid	Major product	Yield[a]
1	 5.4a	 5.2a	 5.5aa	70%
2[b]	 5.4a	 5.2a	 5.5aa'	64%
3	 5.4b	 5.2a	 5.5ba	72%
4	 5.4c	 5.2a	 5.5ca	55%
5	 5.4d	 5.2a	 5.5da	78%
6[c]	 5.4e	 5.2a	 5.5ea	64% 1.3 : 1 regio.
			 5.5ea'	10% **5.5ea'**
7	 5.4f	 5.2a	 5.5fa	27%

8	 5.4a	 5.2i	 5.5ai	67%
9	 5.4b	 5.2j	 5.5bj	85%
10	 5.4b	 5.2k	 5.5bk	63%
11	 5.4b	 5.2l	 5.5bl	59%

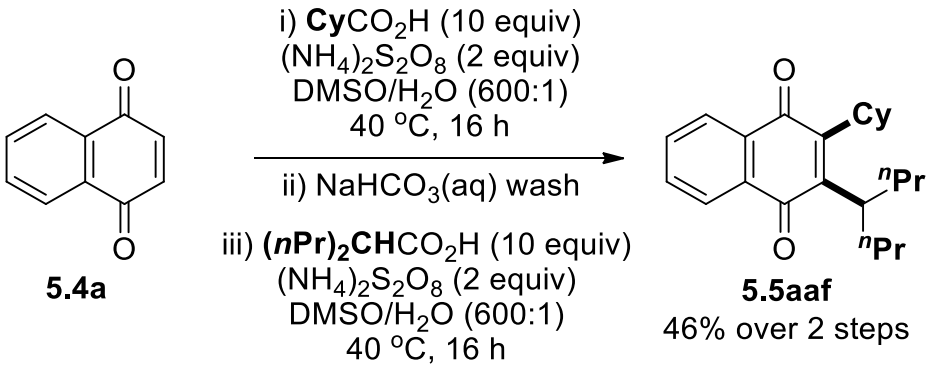
[a] Isolated yields, [b] 20 equiv. of acid, 4 equiv. oxidant and 3 days, [c] 1.3 : 1 mixture of the two regioisomers of **5.5ea** as well as 10% disubstitution (**5.5ea'**).

Table 5.6: Scope for the alkylation of 1,4-quinones

The C-H alkylation of quinones was investigated next. Optimisation of the reaction conditions on 1,4-naphthoquinone **5.4a** (Table 5.1) provided the alkylated product in good yield (**5.5aa**, 70%, Entry 1, Table 5.6) and also showed the potential for dialkylation of 1,4-naphthoquinone **5.4a**. Dialkylation could be achieved by simply increasing the reaction time and equivalents of reagents (**5.5aa'**, 64%, Entry 2, Table 5.6). Moving to other quinones we found that the provitamin menadione **5.4b** and 1,4-anthraquinone **5.4c** also reacted very smoothly under our conditions (**5.5ba** and **5.5ca**, 72% and 78%, Entry 3 and 4, Table 5.6). Pleasingly, 2-methoxy-1,4-naphthoquinone also reacted reasonably well under our conditions (**5.5da**, 55%, Entry 5, Table 5.6) and the hydroxyl group in the 5-position of juglone was tolerated well, albeit with low regioselectivity and some dialkylation being obtained (**5.5ea**, 64% 1.3:1 regio., + **5.5ea'**, 10% Entry 6, Table 5.6). Disappointingly, the parent 1,4-benzoquinone was not as well suited to our conditions (**5.5fa**, 27%, Entry 7, Table 5.6) but we were overall very pleased with the range of the quinones which could be alkylated, especially given the moiety's prevalence in nature. We next investigated the scope of carboxylic acids which could be used for the alkylation of 1,4-quinones by coupling both tertiary and primary carboxylic acids with menadione **5.5b**. To our surprise, pivalic acid did not

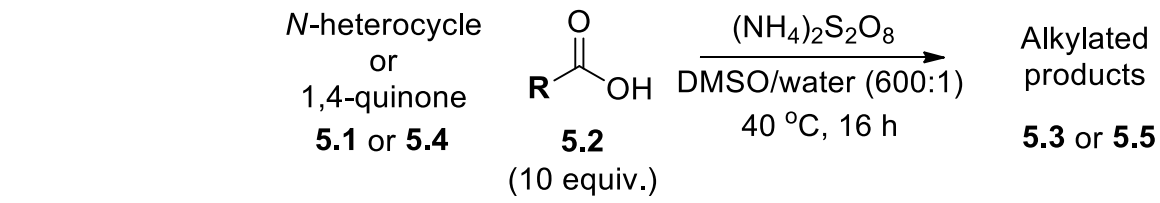
react well with menadione **5.5b** giving only trace product. Gratifyingly, reaction with 1,4-naphthoquinone **5.5a** proceeded much more smoothly providing **5.5ai** in good yield (67%, Entry 8, Table 5.6) and suggesting that coupling with menadione **5.5b** was problematic due to steric hindrance. Pleasingly, primary carboxylic acids reacted well under our conditions with the addition of a benzyl group occurring with excellent yield (**5.5bj**, 85%, Entry 9, Table 5.6), propionic acid reacting smoothly (**5.5bk**, 63%, Entry 10, Table 5.6) and the alkyne functionality being tolerated well in the formation of product **5.5bl** (59%, Entry 11, Table 5.6). These yields are a big improvement on the lower yields obtained using primary carboxylic acids during our initial carboxylic acid screen with *N*-heteroarene **5.1b** (Entries 10-12, Table 5.5), showing that the performance of the primary carboxylic acids is substrate dependent.

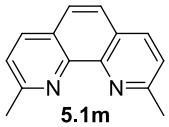
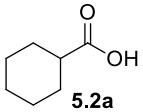
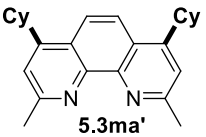
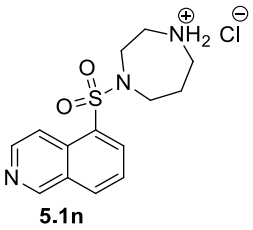
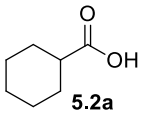
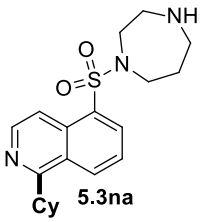
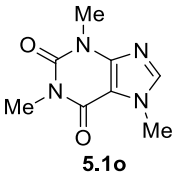
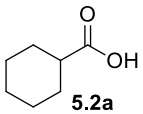
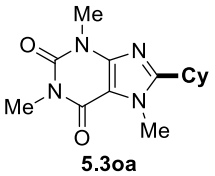
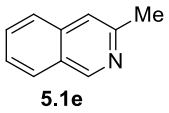
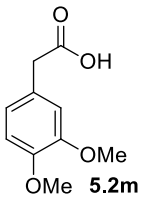
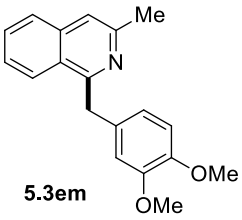
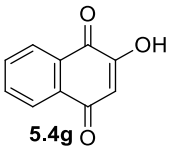
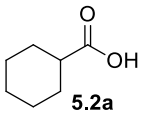
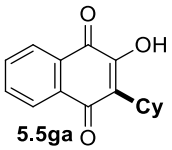
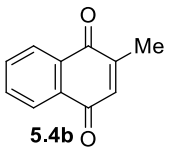
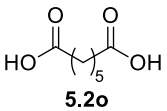
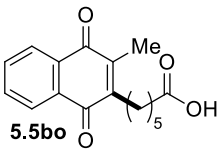
In order to take full advantage of the potential of 1,4-naphthoquinone **5.4a** to be dialkylated, we developed conditions to add two different acids without the need for isolation of the intermediate **5.5aa**. To our delight, after the first alkylation the excess carboxylic acid $CyCO_2H$ **5.2a** can be simply washed out of the crude reaction mixture before the addition of a second acid $(^nPr)_2CHCO_2H$ **5.2f** to give the dialkylated product **5.5aaf** in 46% yield over the two steps (Scheme 5.15).



Scheme 5.15: Rapid dialkylation using different carboxylic acids

5.3.5 Late-stage C-H alkylation



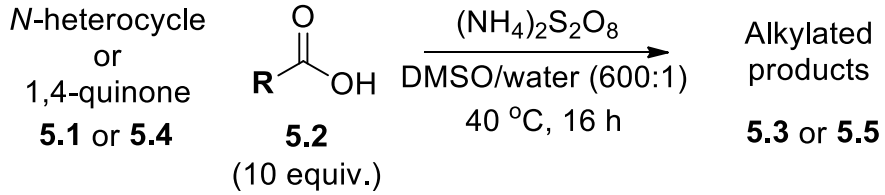
Entry	Substrate	Carboxylic acid	$(NH_4)_2S_2O_8$ (equiv.)	Major product	Yield[a]
1	 5.1m	 5.2a	3	 5.3ma'	82%
2[b]	 5.1n	 5.2a	4	 5.3na	44%
3[c]	 5.1o	 5.2a	3	 5.3oa	28%
4	 5.1e	 5.2m	4	 5.3em	86%
5	 5.4g	 5.2a	2	 5.5ga	33%
6	 5.4b	 5.2o	2	 5.5bo	61%

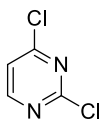
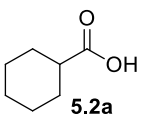
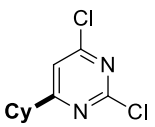
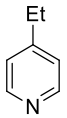
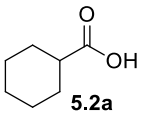
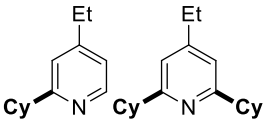
[a] Isolated yields, [b] half normal scale, isolated product impure (90% purity), [c] 40 hours.

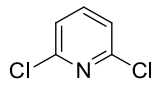
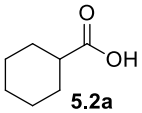
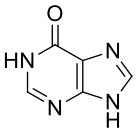
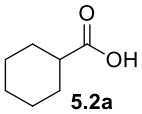
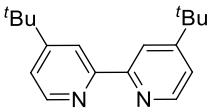
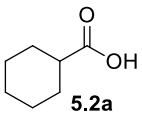
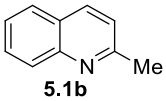
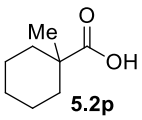
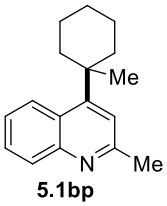
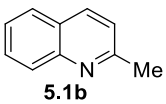
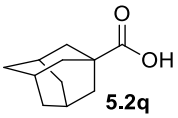
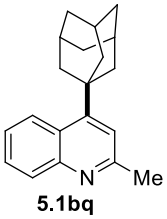
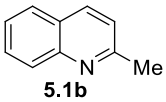
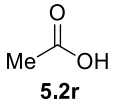
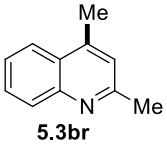
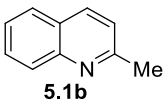
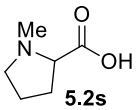
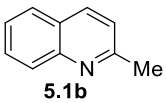
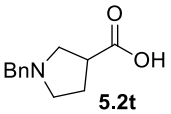
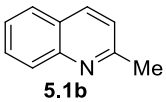
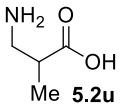
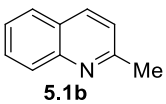
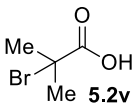
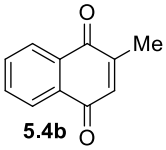
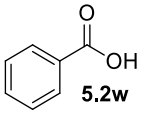
Table 5.7: Late-stage C-H alkylation

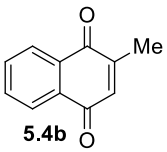
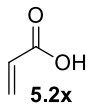
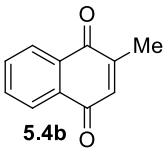
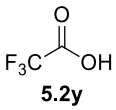
Having shown that our conditions are amenable to a range of *N*-heteroarenes, quinones and carboxylic acids we looked to achieve late-stage C-H functionalisation of more complex substrates (Table 5.7). First, neocuproine **5.1m**, a commonly used ligand in transition metal catalysis, was successfully dialkylated in excellent yield (**5.3ma'**, 82%, Entry 1, Table 5.7). The more complex fasudil.HCl **5.1n**, a well know rho-kinase inhibitor and vasodilator, was functionalised next (**5.3na**, 44%, Entry 2, Table 5.7) and the less reactive caffeine **5.1o** was also successfully alkylated, albeit in a lower yield (**5.3oa**, 28%, Entry 3, Table 5.7). To our delight, we were also able to prepare an analogue of the antispasmodic drug papaverine under our conditions, coupling 3-methylisoquinoline **5.1e** with homoveratric acid **5.2m** in an excellent yield (**5.3em**, 86%, Entry 4, Table 5.7). Parvaquone **5.5ga**, which is marketed as Clexon® for the treatment of cattle, was also successfully prepared by the alkylation of lawsone **5.4g** with carboxylic acid **5.2a** (**5.5ga**, 33%, Entry 5, Table 5.7). Finally, compound **3bo**, which is reported to bind and inhibit glutathione reductase, a targeted enzyme in the treatment of malaria,[171] was also successfully prepared by coupling menadione **5.4b** and pimelic acid **5.2o** (**5.5bo**, 59%, Entry 6, Table 5.7). The preparation of **5.5bo** also shows the conditions are tolerant to a second carboxylic acid group, which remains intact in the reaction.

5.3.6 Substrates and carboxylic acids unsuited to the reaction



Entry	Substrate	Carboxylic acid	$(NH_4)_2S_2O_8$ (equiv.)	Major product	NMR Yield[a]
1	 **5.1p**	 **5.2a**	4	 **5.3pa**	<30%
2	 **5.1q**	 **5.2a**	6	 **5.3qa** **5.3qa'**	**5.3qa** 31% **5.3qa'** 13%

3	 **5.1r**	 **5.2a**	3	No product	-
4	 **5.1s**	 **5.2a**	3	No product	-
5	 **5.1t**	 **5.2a**	3	No product	-
6	 **5.1b**	 **5.2p**	3 6	 **5.1bp**	<20% <20%
7[Д]	 **5.1b**	 **5.2q**	3	 **5.1bq**	36%
8[Д]	 **5.1b**	 **5.2r**	3	 **5.3br**	15%
9[Д]	 **5.1b**	 **5.2s**	3	No product	-
10[Д]	 **5.1b**	 **5.2t**	3	No product	-
11[Д]	 **5.1b**	 **5.2u**	3	No product	-
12[Д]	 **5.1b**	 **5.2v**	3	No product	-
13[Ж]	 **5.4b**	 **5.2w**	2	No product	-

14[π]	 **5.4b**	 **5.2x**	2	No product	-
15[π]	 **5.4b**	 **5.2y**	2	No product	-

[a] Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard, the NMR signals integrated matched literature signals as the products were not isolated.

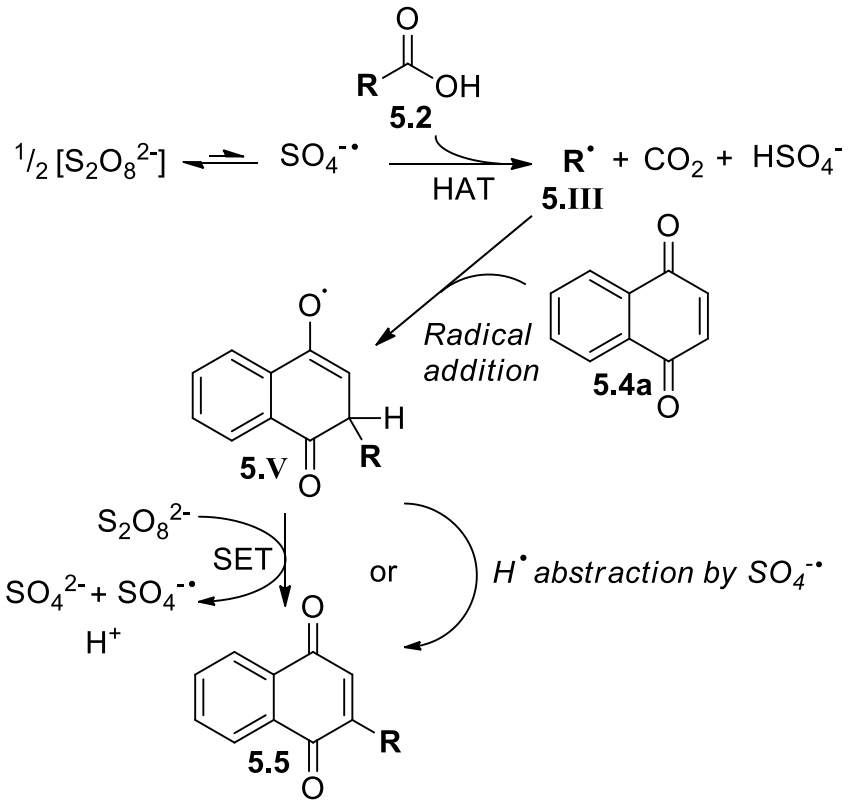
Table 5.8: Substrates and carboxylic acids unsuited to the reaction

Although the alkylation procedure developed was found to be tolerant to a large scope of carboxylic acids, *N*-heteroarenes and 1,4-quinones there were several substrates and acids which were found not to be suited to our conditions. 2,4-Dichloropyrimidine **5.1p** and 4-ethylpyridine **5.1q** were found to react very sluggishly giving low NMR yields of the desired products **5.3pa** and **5.3qa** (<30% and 31%, Entries 1 and 2, Table 5.8). Disappointingly, 2,6-dichloropyridine **5.1r**, which was expected to react similarly to 2,6-lutidine **5.1j** (**5.3ja**, 50%, Entry 10, Table 5.4), preformed worse still, providing no product under our conditions (Entry 3, Table 5.8). Hypoxanthine **5.1s** was also found to be totally unreactive (Entry 4, Table 5.8), as was the common ligand **5.1t** (Entry 5, Table 5.8) although this may have been caused by **5.1t** being insoluble in DMSO.

Some carboxylic acids investigated were also found to be unsuited to the alkylation procedure, including the tertiary carboxylic acids **5.2p** and **5.2q** which gave much lower yields (**5.3bp** and **5.3bq**, <20% and 36%, Entries 6 and 7, Table 5.8) when compared to pivalic acid **5.2i** (**5.3bi**, 61%, Entry 9, Table 5.5). Acetic acid **5.2r** was also found to perform poorly (**5.3br**, 15%, Entry 8, Table 5.8) and *N*-methylproline **5.2r** provided no product in the reaction (Entry 9, Table 5.8). **5.2r** being unreactive was thought to be due to the radical being formed *alpha* to the nitrogen. However, *N*-benzyl-*beta*-proline was also totally unreactive under our conditions (Entry 10, Table 5.8). Interestingly, the unprotected amine containing carboxylic acid **5.2u** was not tolerated in the reaction (No reaction, Entry 11, Table 5.8) despite the protected amino acid **5.2d** reacting very cleanly (91%, **5.3bd**, Entry 4, Table 5.5). Bromine containing carboxylic acid **5.2v** was also not tolerated in the reaction presumably due to the

reactivity of the bromo-group (Entry 12, Table 5.8). Finally, carboxylic acids **5.2w**, **5.2x** and **5.2y** were found to be totally unreactive under our alkylation procedure perhaps due to the very different nature of the radicals generated (Entry 12-15, Table 5.8).

5.3.7 Mechanistic studies

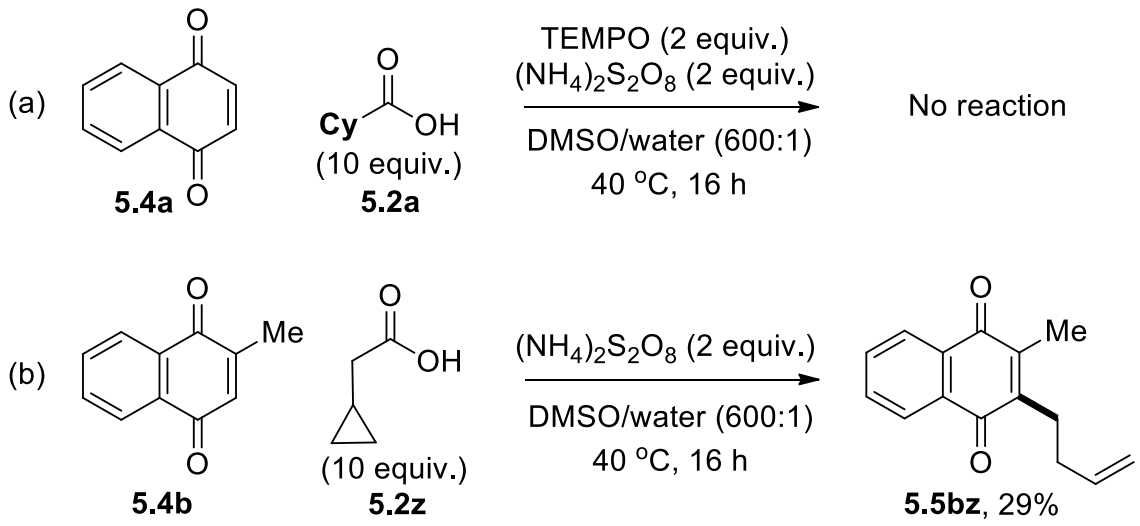


Scheme 5.16: Proposed mechanism for the alkylation of *N*-heteroarenes and 1,4-quinones

Our proposed mechanism (Scheme 5.16) begins with the homolysis of the persulfate to the radical sulfate anion which would usually be slow at the temperatures used in our procedure (30-40 °C). However, the rate at which homolysis of $S_2O_8^{2-}$ occurs is reported to be dependent on solvent,[169] and is known to be much faster in DMSO,[170] also explaining why the use of DMSO as a solvent is crucial to the reaction (Table 5.3). The radical sulfate anion is therefore thought to be produced at rate fast enough to sustain the reaction without the need for a metal, light or a photocatalyst. Once generated, the radical sulfate anion undergoes hydrogen atom transfer (HAT) with the carboxylic acid causing decarboxylation and providing the alkyl radical **5.III**. Radical addition to the substrate **5.4a** then gives intermediate **V** which can be converted to

the product **5.5** by two possible mechanisms. The first of these is single electron oxidation using another equivalent of persulfate and deprotonation. Alternatively, the product **5.5** could be formed from intermediate **V** by radical H extraction by a radical sulfate anion.

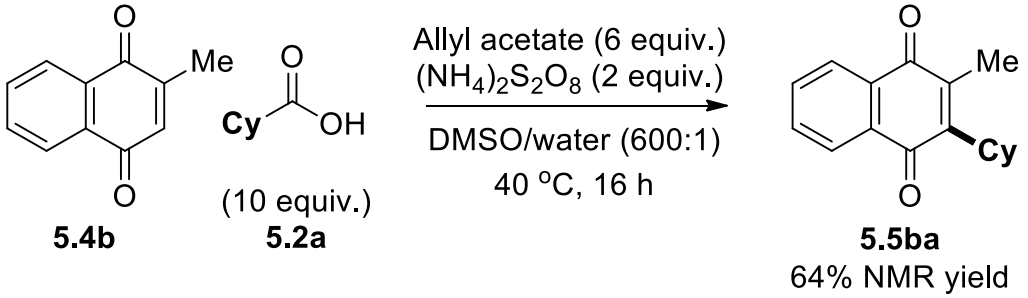
In order to gain evidence for the proposed mechanism we first looked to show that the reaction was proceeding through a radical pathway. Addition of radical trap TEMPO totally retarded the reaction ((a), Scheme 5.17) and coupling of menadione **5.4b** and 2-cyclopropylacetic acid **5.2z** gave the ring opened product **5.5bz** ((b), Scheme 5.17) suggesting radicals are indeed involved in the mechanism.



Scheme 5.17: Experiments suggesting a radical mechanism

Having shown that the reaction proceeds through a radical mechanism, the involvement of the radical sulfate anion was investigated next using allyl acetate. Allyl acetate is known to sequester radical sulfate anions and so should slow down the reaction if radical sulfate anions are involved directly in the mechanism.[169, 172] Adding 6 equivalents of allyl acetate reduced the yield of the alkylation of both 1,4-naphthoquinone **5.4b** (Scheme 5.18) and quinaldine **5.1b** (Scheme 5.19). However, the drop in yield was deemed to be not substantial enough to prove that allyl acetate was having an effect on the reaction and so further investigation was carried out. Aliquots of the reaction both with and without allyl acetate were taken at various time points, providing the % conversion over time for the alkylation of quinaldine **5.1b**

(Table 5.10 and Figure 5.6). The data clearly indicates that allyl acetate is having an effect on the rate of the reaction and further experiments using a large excess of allyl acetate (Scheme 5.20) and investigating the effect of allyl acetate at 30 ^{o}C (Scheme 5.21) also indicate that allyl acetate is having a negative effect on the reaction.

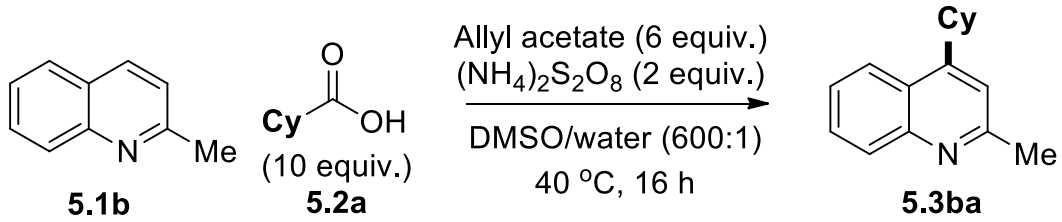


5.4b **5.2a** **5.5ba**

64% NMR yield

Isolated yield without allyl acetate 72%

Scheme 5.18: Effect of 6 equiv. allyl acetate on the alkylation of **5.4b**[a]

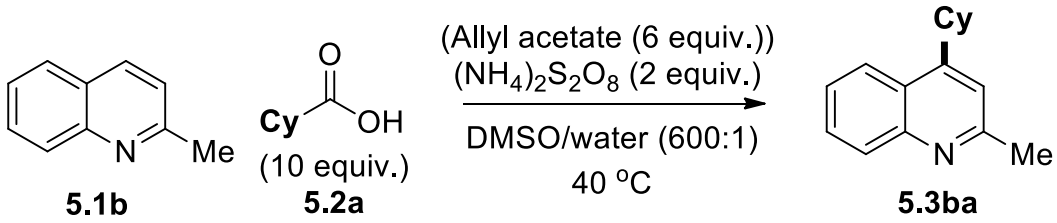


5.1b **5.2a** **5.3ba**

70% NMR yield

Isolated yield without allyl acetate 80%

Scheme 5.19: Effect of 6 equiv. allyl acetate on the alkylation of **5.1b**



5.1b **5.2a** **5.3ba**

Time (h)	% conv. by NMR	
	Normal conditions	6 equiv. allyl acetate added
1	16	8
2	31	21
3	50	31
5	73	41
8	81	64

Table 5.10: Effect of allyl acetate on the alkylation of **5.1b** over time

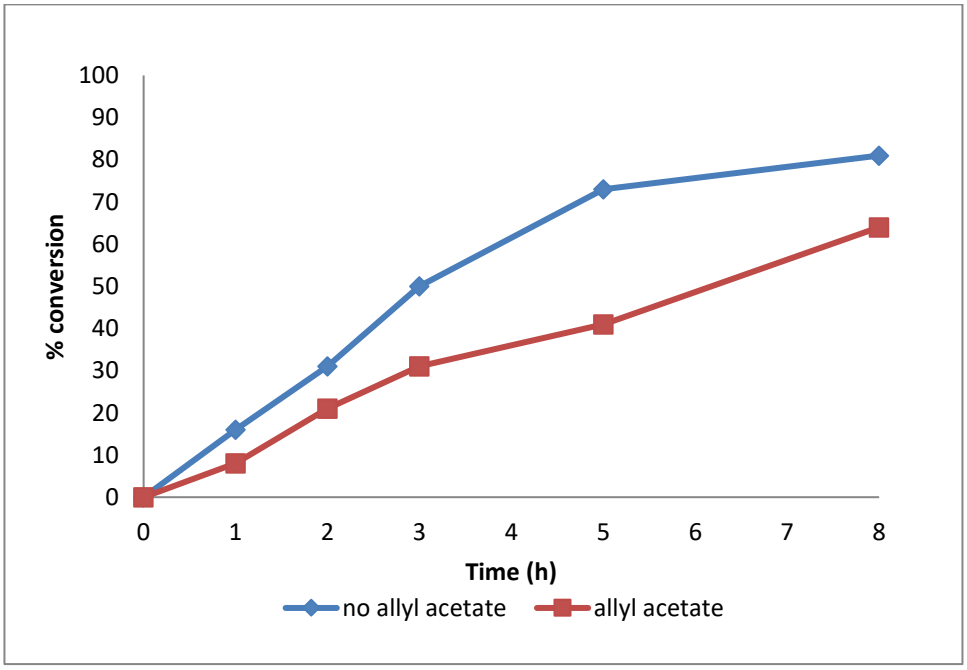
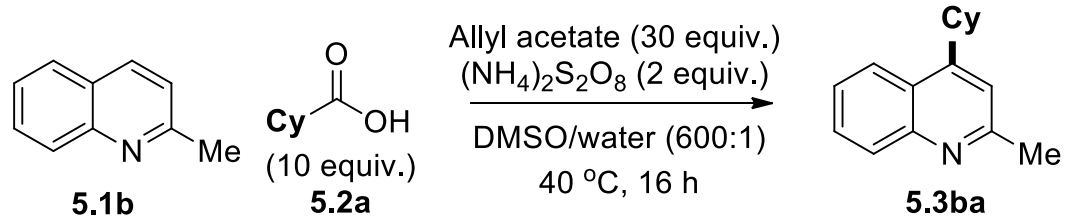


Figure 5.6: Effect of allyl acetate on the alkylation of **5.1b** over time

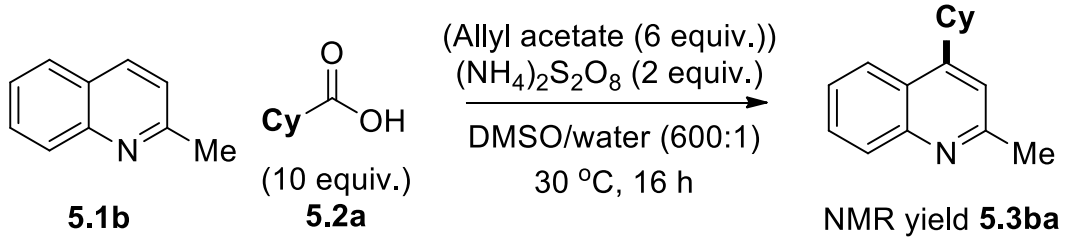


5.1b **5.2a** **5.3ba**

44% NMR yield

Isolated yield without allyl acetate 80%

Scheme 5.20: Effect of 30 equiv. allyl acetate on the alkylation of **5.1b**



5.1b **5.2a**

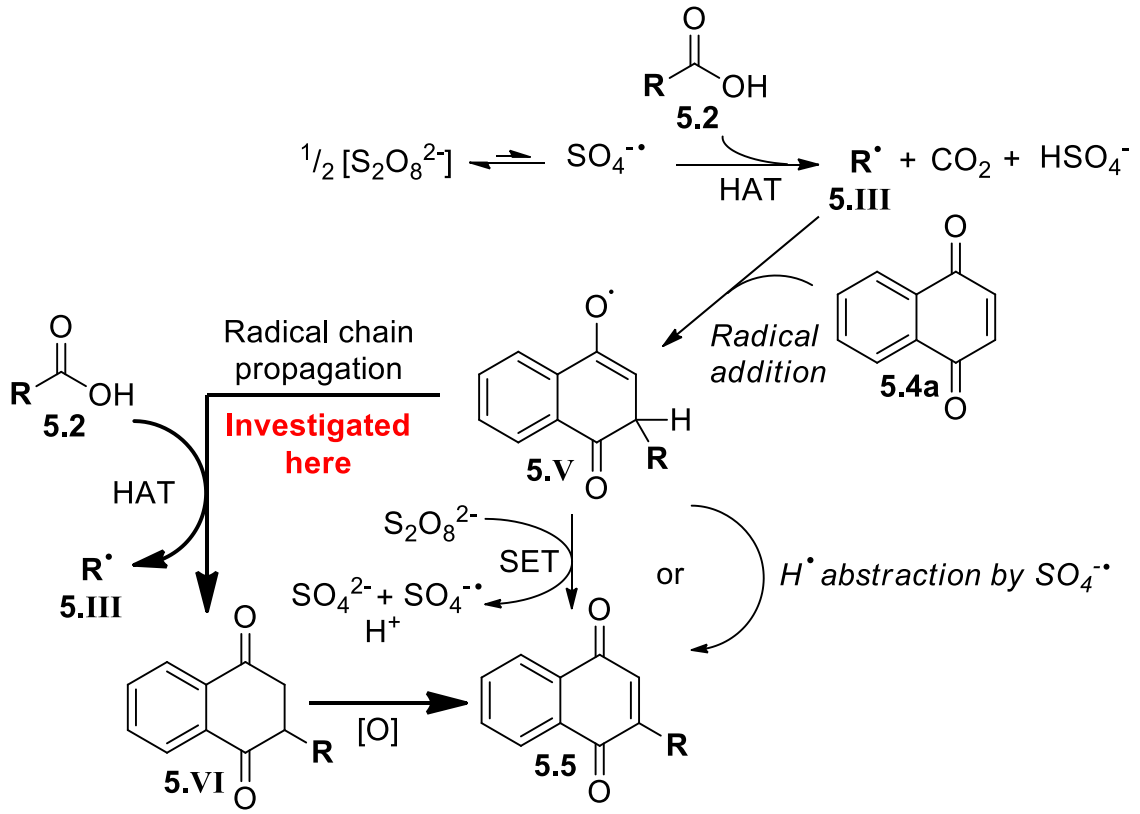
NMR yield **5.3ba**

With allyl acetate 56%

Without allyl acetate 73%

Scheme 5.21: Effect of 6 equiv. allyl acetate on the alkylation of **5.1b** at 30 °C

Since the evidence suggests that the addition of allyl acetate slows the alkylation we can conclude that the radical sulfate anion is, as proposed (Scheme 5.16), involved in the reaction mechanism. The final piece of mechanistic investigation done was the study of an alternative pathway for the conversion of intermediate **5.V** to the product **5.5** via intermediate **5.VI** (Scheme 5.22).

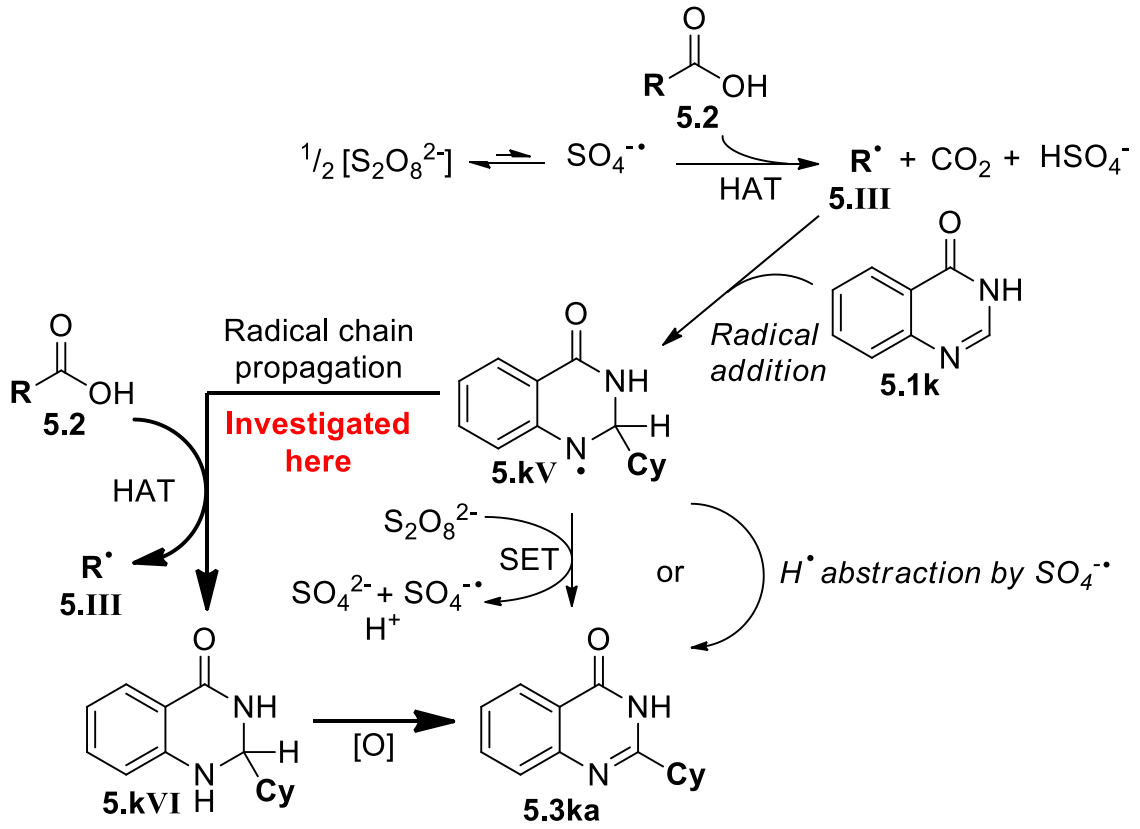


Scheme 5.22: Alternative mechanistic pathway (found to be unlikely)

In addition to the two pathways by which **5.V** can be converted to the product **5.5** previously discussed, there is also the possibility of a third radical chain propagation pathway (bold arrows, Scheme 5.22). This pathway (along with the SET with persulfate) can be considered a radical chain propagation pathway, as the generation of the radical sulfate anion by homolysis is not required for this pathway to propagate. In this third proposed pathway which is similar to the mechanism proposed by Molander and co-workers in their alkylation procedure using 1,4-dihydropyridines,[162] intermediate **5.V** abstracts a radical H from the carboxylic acid **5.2** generating another alkyl radical which can go on to react with another equivalent of substrate **5.4a**.

In order to investigate the possibility of this alternative pathway (Scheme 5.22), we attempted to detect intermediate **5.VI**. This was unlikely to be possible using 1,4-naphthoquinone **5.4b** as a substrate as it was thought that intermediate **5.VI** would be too readily oxidised. However, since the intermediate **5.kVI** is easily synthesised by other means (see Section 5.5.6) and a similar compound was detected

by Molander and co-workers in their alkylation procedure,[164] substrate **5.1k** could be used for this investigation (Scheme 5.23).



Scheme 5.23: Alternative mechanistic pathway for **5.1k** (found to be unlikely)

Using HPLC as the detection method, the reaction mixture was analysed at various time points and using different amounts of oxidant but the intermediate **5.kVI** could not be detected (Figures 5.7 and 5.8). Since Molander and co-workers previously detected a similar intermediate in their alkylation protocol and did so using the same method,[164] it was concluded that intermediate **5.VI** is not forming under our reaction conditions. Since intermediate **5.VI** is not detectable in our reaction mixture this alternative pathway is thought to be unlikely under our conditions.

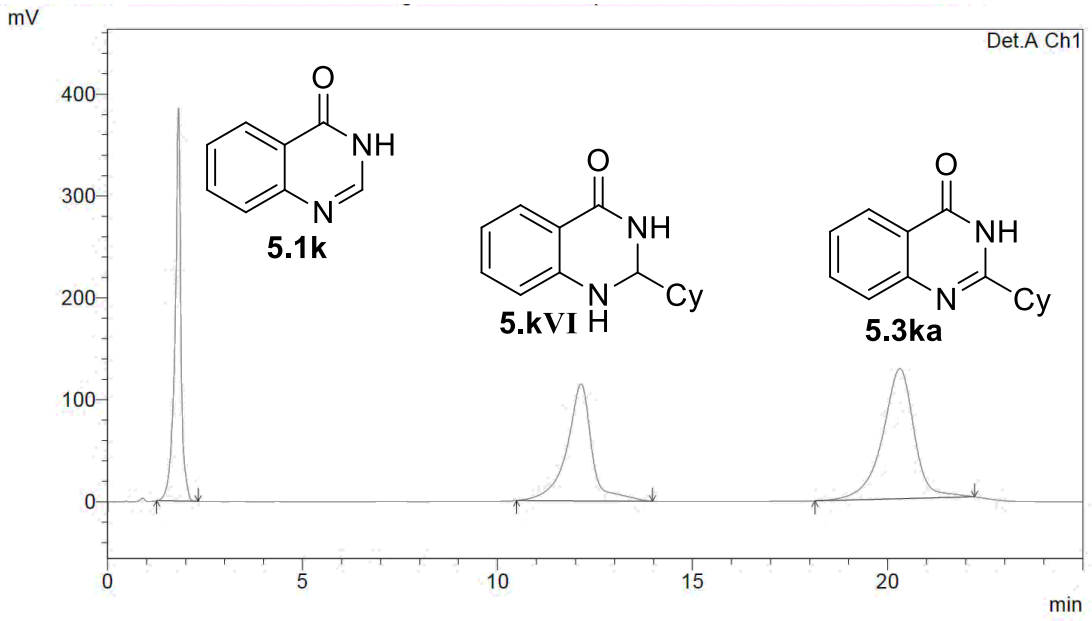
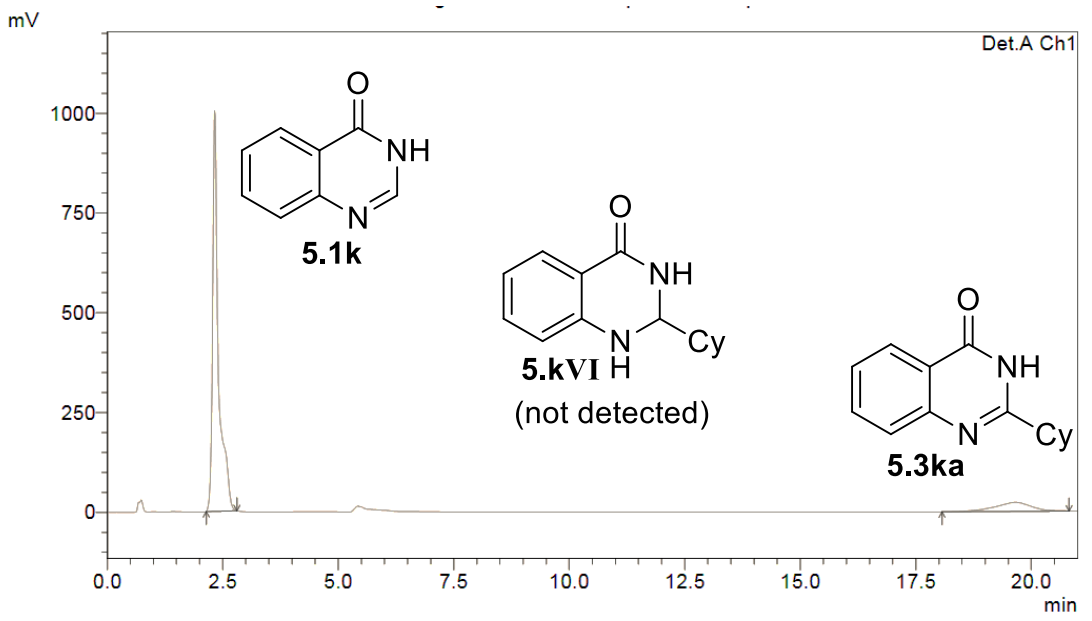


Figure 5.7: HPLC trace of a mixture of starting material **5.1k**, intermediate **5.kVI** and product **5.3ka**.



HPLC (LUNA 5µ C18(2), 1:1 MeOH:H_2O, 1.75 ml min^{-1})

Figure 5.8: Example HPLC trace of reaction mixture (1 equiv. of oxidant, 3 h)

5.4 Conclusions

The first metal-, light- and photocatalyst free alkylation procedure using carboxylic acids has been developed and has been shown to be suitable for the late-stage C-H functionalisation of *N*-heteroarene and 1,4-quinone moieties. The reaction is particularly useful as it does not require expensive photocatalysts or metals, uses cheap and readily available carboxylic acids and does not require irradiation. The development of light-free conditions was of particular importance as it allowed for the alkylation of 1,4-quinones which, during the optimisation of the reaction, were shown to degrade under blue light irradiation.

The mild Minisci-type conditions developed allows for the generation of alkyl radicals without the previously employed metal, photocatalyst, light or prefunctionalisation. This is thought to be thanks to DMSO increasing the rate of persulfate homolysis,[170] a key step in the proposed mechanism. The thermal homolysis of persulfate is reported to occur at higher temperatures (>70 ^{o}C)[169] but the use of DMSO as a solvent makes this possible under much milder conditions, allowing for late-stage C-H alkylation of medicinally relevant compounds. As well as medicinally relevant compounds, a range of *N*-heteroarenes and 1,4-quinones were functionalised and primary, secondary and tertiary carboxylic acids were all tolerated.

5.5 Experimental

5.5.1 General considerations

^{1}H NMR spectra were recorded on a Bruker AV300 or AV400 spectrometer at 300 MHz or 400 MHz respectively. ^{13}C NMR spectra were recorded using the same spectrometers at 75 MHz or 100 MHz respectively. Chemical shifts (δ in ppm) were referenced to tetramethylsilane (TMS) or to residual solvent peaks ($CDCl_3$ at δ_H 7.26 ppm and δ_C at 77.0 ppm and CD_3CN at δ_H 2.13, 1.94 ppm and δ_C at 116.3, 1.3 ppm). ^{19}F NMR spectra were recorded on a Bruker AV400 spectrometer at 376 MHz. *J* values are given in Hz and br., s, d, t, q, quin, sext, sept, m, are abbreviations corresponding to broad, singlet, doublet, triplet, quartet, quintet, sextuplet, septuplet, multiplet respectively or a combination of these. Mass spectra were obtained from the EPSRC UK National Mass Spectrometry Facility at Swansea University. Infrared spectra were obtained on Perkin-Elmer Spectrum 100 FT-IR Universal ATR Sampling Accessory, deposited neat to a diamond/ZnSe plate.

Column chromatography was carried out using Matrix silica gel 60 from Fluorochem or neutral alumina Brockmann I 50-200 µm 60 from Acros Organics. TLC performed using Merck silica gel 60 F254 or Aluminium oxide 60 F254 neutral pre-coated sheets and visualised by UV (254 nm) or stained by the use of aqueous acidic $KMnO_4$. Chemicals were purchased from Sigma-Aldrich, Acros, Apollo Scientific, Fisher, Fluorochem, Alfa Aesar, TCI and Manchester Organics chemical companies and either used without further purification or purified by recrystallisation (menadione, 1,4-anthraquinone, 2-hydroxy-1,4-naphthoquinone, quinazoline, phthalazine and 4-hydroxyquinazoline) or sublimation (1,4-benzoquinone and 1,4-naphthoquinone).

High performance liquid chromatography (HPLC) was carried out on a Shimadzu LC-20AD.

5.5.2 General procedure for alkylation reaction

General procedure A

To a nitrogen or argon backfilled Schlenk tube substrate **5.1** or **5.4** (0.15 mmol, 1 equiv.), carboxylic acid **5.2** (1.50 mmol, 10 equiv.) and ammonium persulfate were added. After a final backfill, DMSO/water (3mL/5 µL degassed by bubbling with argon (2 balloons/15 mins) was added and the reaction was sealed and stirred overnight at 40 ^{o}C.

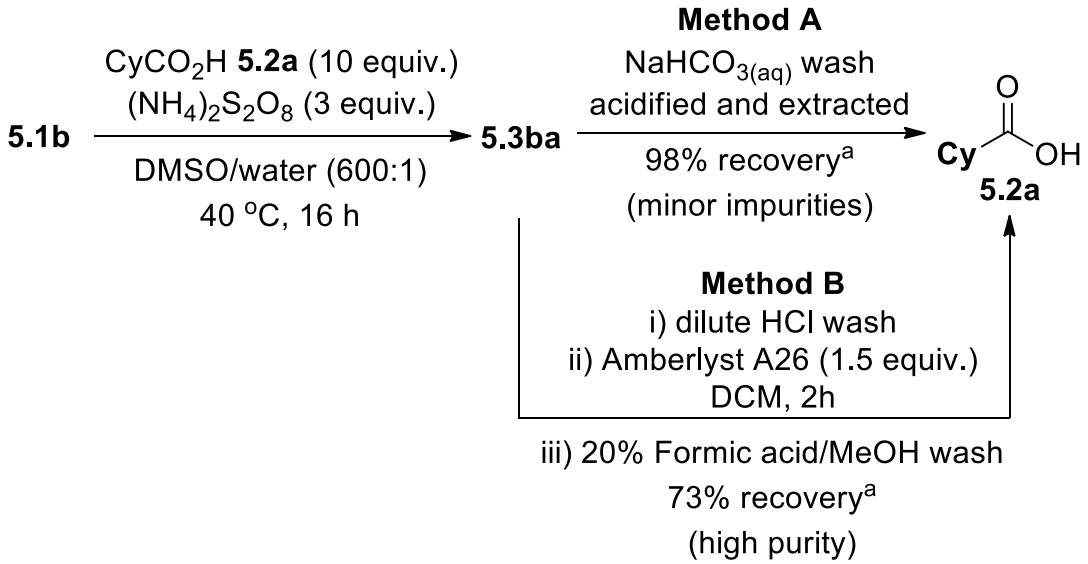
The reaction mixture was diluted with DCM (15 mL) and washed with sat. $NaHCO_3$ solution. The aqueous layer was then extracted with DCM (2 x 15 mL) and the combined organic layers were washed with brine (40 mL), dried (Na_2SO_4) and concentrated to give the crude product.

General procedure B

Heteroarene **5.1** (0.15 mmol, 1 equiv.) was weighed into a small RBF before being transferred to a nitrogen or argon backfilled Schlenk tube with DMSO/water (3 mL/5 µL, degassed by bubbling with argon). After 5 minutes of bubbling with argon, carboxylic acid **5.2** (1.50 mmol, 10 equiv.) and ammonium persulfate were added, and the reaction was sealed and stirred overnight at 40 ^{o}C.

The reaction mixture was diluted with DCM (15 mL) and washed with sat. $NaHCO_3$ solution. The aqueous layer was then extracted with DCM (2 x 15 mL) and the combined organic layers were washed with brine (40 mL), dried (Na_2SO_4) and concentrated to give the crude product.

5.5.3 Procedure for carboxylic acid recovery



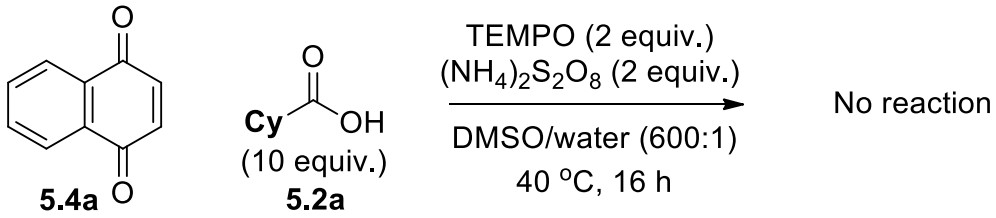
[a]NMR yields based on potential recovery of 9 equiv.

Quinaldine **5.1b** (21.5 mg, 0.15 mmol, 1 equiv.) was weighed into a small RBF before being transferred to a nitrogen or argon backfilled Schlenk tube with DMSO/water (3 mL/5 µL, degassed by bubbling with argon). After 5 minutes of bubbling with argon, cyclohexanecarboxylic acid **5.2a** (192 mg, 1.50 mmol, 10 equiv.) and ammonium persulfate (103 mg, 0.45 mmol, 3 equiv.) were added and the reaction was sealed and stirred overnight at 40 °C.

Method A: The reaction mixture was diluted with DCM (15 mL) and washed twice with sat. $NaHCO_3$ solution. The aqueous layer was then acidified to pH 1 with dilute $HCl_{(aq)}$ and extracted with DCM (3 x 20mL) and the combined organic layers were washed with brine (40 mL), dried (Na_2SO_4) and concentrated under reduced pressure. 1,3,5-Trimethoxybenzene (8.4mg, 0.05 mmol, 0.33 equiv.) was added as an internal standard and the ^{1}H NMR yield was taken.

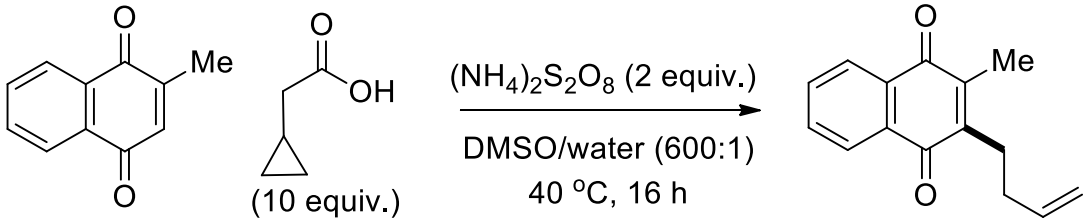
Method B:[173, 174] The reaction mixture was diluted with DCM (40 mL) and washed with very dilute $HCl_{(aq)}$ and then brine. The combined aqueous layers were extracted with DCM and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude mixture was redissolved in DCM (15 mL) and stirred for 2 hours with Amberlyst A26 (1.68 g, 2.25 mmol, 15 equiv.). The Amberlyst A26 was filtered off and washed with MeOH to give the crude product **5.3ba**. The Amberlyst A26 was then washed again with 20% formic acid in MeOH and the filtrate was concentrated under reduced pressure. 1,3,5-Trimethoxybenzene (8.4mg, 0.05 mmol, 0.33 equiv.) was added as an internal standard and the ^{1}H NMR yield was taken.

5.5.4 Mechanistic studies – evidence for radical mechanism



5.4a **5.2a**

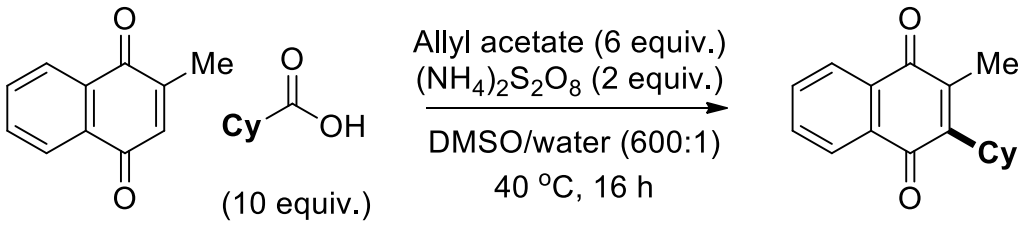
Following general procedure A, 1,4-naphthoquinone **5.4a** (23.7 mg, 0.15 mmol, 1 equiv.), cyclohexanecarboxylic acid **5.2a** (192 mg, 1.50 mmol, 10 equiv.) and ammonium persulfate (68.5 mg, 0.30 mmol, 2 equiv.), with the addition of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (46.9 mg, 0.30 mmol, 2 equiv.) were allowed to stir at 40 °C and after 16 h, the NMR of the crude reaction mixture showed no desired product and unreacted starting material **5.4a**.



5.4b **5.2z** **5.5bz**, 29%

General procedure A was followed, reacting menadione and cyclopropylacetic acid to give solely the ring opened product **5.5bz**. Full characterisation in Section 5.5.7.

5.5.5 Mechanistic studies – allyl acetate

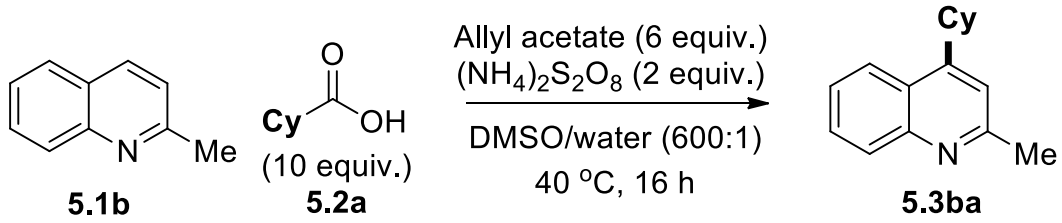


5.4b **5.2a** **5.5ba**
64% NMR yield

Isolated yield without allyl acetate 72%

Following general procedure A menadione **5.4b** (25.8 mg, 0.15 mmol, 1 equiv.), cyclohexanecarboxylic acid **5.2a** (192 mg, 1.50 mmol, 10 equiv.) and ammonium persulfate (68.5 mg, 0.30 mmol, 2 equiv.) were added to the Schlenk flask. Allyl acetate (79 μL, 0.90 mmol, 6 equiv.) was added immediately after DMSO/water was added. ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethoxybenzene as an

internal standard showed the NMR yield of **5.5ba** to be 64%, slightly lower than the isolated yield without allyl acetate (72%).

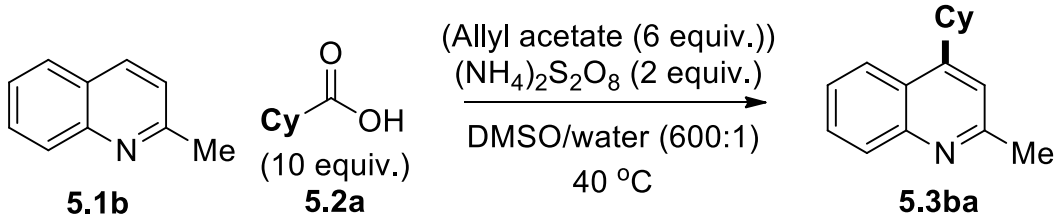


5.1b **5.2a** **5.3ba**

70% NMR yield

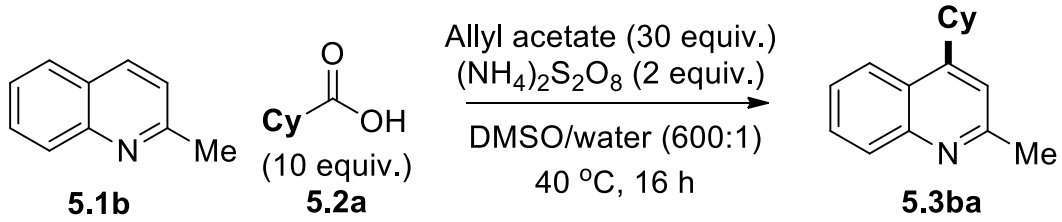
Isolated yield without allyl acetate 80%

Under Schlenk conditions, to quinaldine **5.1b** (21.5 mg, 0.15 mmol, 1 equiv.) and allyl acetate (97µL, 0.90 mmol, 6 equiv.), in argon bubbled DMSO/water (3mL/5µL), was added cyclohexanecarboxylic acid **5.2a** (192 mg, 1.50 mmol, 10 equiv.) and ammonium persulfate (103 mg, 0.45 mmol, 3 equiv.). The reaction mixture was briefly bubbled with argon, sealed and stirred overnight at 40 °C. ^{1}H NMR of the crude reaction mixture with 1,3,5-trimethoxybenzene as an internal standard showed the yield of **5.3ba** (70%) to be slightly lower than under the standard conditions without allyl acetate (82% isolated yield).



5.1b **5.2a** **5.3ba**

Further investigation was carried out by running two experiments in tandem - one with allyl acetate and one without. The experiments were set up as detailed above and aliquots were taken at the time points shown below. The percentage conversion was determined by ^{1}H NMR.

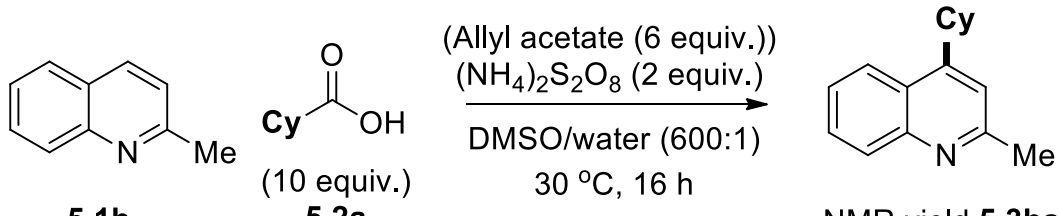


5.1b **5.2a** **5.3ba**

44% NMR yield

Isolated yield without allyl acetate 80%

The reaction was carried out as above with a greater excess of allyl acetate (486 µL, 4.50 mmol, 30 equiv.) giving **5.3ba** in a NMR yield of 44% with 29% starting material **5.1b** remaining.



5.1b **5.2a**

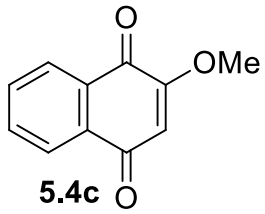
NMR yield **5.3ba**

With allyl acetate	56%
Without allyl acetate	73%

The reaction was also carried out as detailed above but at 30 °C, showing a lower yield with allyl acetate at this temperature.

5.5.6 Starting material and intermediate synthesis

2-Methoxynaphthalene-1,4-dione (5.4c)[175]

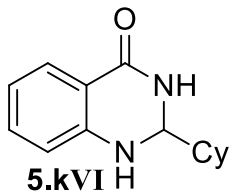


5.4c

Concentrated sulphuric acid (75 µL) was added to 2-hydroxy-1,4-naphthoquinone (296 mg, 1.70 mmol) in methanol (15 mL) and refluxed overnight. The reaction mixture was neutralised with 2M NaOH(aq), concentrated under vacuum, redissoved in DCM and dried (Na_2SO_4). The crude product was concentrated and purified by column chromatography (eluent: 5:1 to 2:1 petrol 40-60 °C/EtOAc) to yield product **5.4c** as a white solid (258 mg, 1.37 mmol, 81%).

R_F 0.29 (2:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 3050, 2956, 2853 (C-H), 1680, 1644 (C=O), 1605, 1591, 1577, 1445 (C-C Ar); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.18 – 8.04 (2H, m, Ar-H), 7.81 – 7.65 (2H, m, Ar-H), 6.18 (1H, s, =CH), 3.91 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.0 (C), 180.3 (C), 160.6 (C), 134.5 (CH), 133.5 (CH), 132.2 (C), 131.2 (C), 126.9 (CH), 126.4 (CH), 110.1 (CH), 56.6 (CH_3); m.p. = 183 °C (lit.[176] 182-183 °C).

2-Cyclohexyl-2,3-dihydroquinazolin-4(1H)-one (5.kVI)



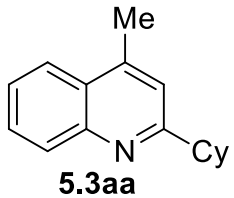
5.kVI

Following an adapted procedure[164] 2-aminobenzamide (136 mg, 1.0 mmol) and cyclohexanecarbaldehyde (363 µL, 3 mmol) were refluxed in 2,2,2-trifluoroethanol (2.5 mL) under an argon atmosphere for 45 minutes. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (eluent: 2:1 to 1:2 petrol 40-60 °C/EtOAc) to yield product **5.kVI** as a white solid (210 mg, 0.98 mmol, 98%).

R_F 0.29 (1:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 3364, 3166 (N-H), 3055, 2921, 2850 (C-H), 1642 (C=O), 1609, 1503, 1484 (C-C Ar); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.87 (1H, dd, *J*=7.8, 1.6 Hz, Ar-H), 7.34 – 7.23 (1H, ddd, J=8.2, 7.5, 1.6 Hz, Ar-H), 6.82 (1H, app. td, *J*=7.5, 1.0 Hz, Ar-H), 6.65 (1H, dd, *J*=8.2, 1.0 Hz, Ar-H), 6.20 (1H, br. S, NH), 4.64 (1H, dd, *J*=5.1, 1.6 Hz, NHCH), 4.26 (1H, br. s, NH), 1.90 – 1.57 (6H, m, alkyl CHs), 1.36 – 1.00 (5H, m, alkyl CHs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3 (C), 147.6 (C), 133.9 (CH), 128.6 (CH), 119.1 (CH), 115.8 (C), 114.6 (CH), 69.7 (CH), 42.8 (CH), 27.7 (CH_2), 27.6 (CH_2), 26.3 (CH_2), 25.91 (CH_2), 25.89 (CH_2); Found (FTMS + p NSI) $[M + H]^+$ 231.1492, $C_{14}H_{19}N_2O$ requires 231.1492; m.p. = 175 °C (lit.[177] 175-176 °C).

5.5.7 Product characterisation

2-Cyclohexyl-4-methylquinoline (5.3aa)

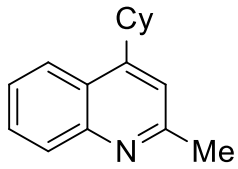


5.3aa

General procedure B was followed, reacting 4-methylquinoline (21.5 mg, 0.15 mmol), cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and ammonium persulfate (103 mg, 0.45 mmol) in DMSO/H_2O (3 mL/5 µL). The crude product was purified by column chromatography (eluent: 80:1 to 30:1 petrol 40-60 °C/EtOAc + 5% toluene) to yield product **5.3aa** as a yellow oil (27.6 mg, 0.12 mmol, 82%).

R_F 0.24 (30:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2923, 2851 (C-H), 1603, 1559, 1507, 1447 (C-C Ar); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.04 (1H, ddd, *J*=8.4, 1.3, 0.6 Hz, Ar-H), 7.94 (1H, dm, *J*=8.2 Hz, Ar-H), 7.66 (1H, ddd, *J*=8.4, 6.9, 1.5 Hz, Ar-H), 7.49 (1H, ddd, *J*=8.2, 6.9, 1.3 Hz, Ar-H), 7.17 (1H, q, *J*=0.9 Hz, Ar-H), 2.87 (1H, tt, *J*=11.9, 3.4 Hz, alkyl CH), 2.68 (3H, d, *J*=0.9 Hz, CH_3), 2.07 – 1.74 (5H, m, alkyl CHs), 1.66 – 1.23 (5H, m, alkyl CHs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7 (C), 147.7 (C), 144.4 (C), 129.6 (CH), 129.1 (CH), 127.2 (C), 125.5 (CH), 123.7 (CH), 120.4 (CH), 47.7 (CH), 33.0 ($2CH_2$), 26.7 ($2CH_2$), 26.3 (CH_2), 19.0 (CH_3); NMR data matches literature values.[160]

4-Cyclohexyl-2-methylquinoline (5.3ba)



5.3ba

General procedure B was followed, reacting 2-methylquinoline (21.5 mg, 0.15 mmol), cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and ammonium persulfate (103 mg, 0.45 mmol) in DMSO/H_2O (3 mL/5 µL). The crude product was purified by column chromatography (eluent: neat to 10:1 petrol 40-60 °C/EtOAc) to yield product **5.3ba** as a colourless oil (27.0 mg, 0.12 mmol, 80%).

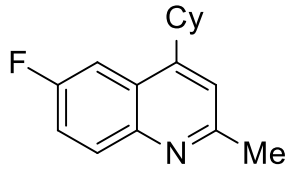
0.5 g Scale experiment.

General procedure B was followed reacting 2-methylquinoline (0.47 mL, 3.49 mmol), cyclohexanecarboxylic acid (4.48 g, 34.9 mmol) and ammonium persulfate (2.39 g, 10.5 mmol) in DMSO/water (69.8 mL/116 µL). The crude product was purified by column chromatography (eluent: 3:1 hexanes/EtOAc) to yield product **5.3ba** as a yellow oil (617 mg, 2.72 mmol, 78%).

R_F 0.25 (5:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2925, 2851 (C-H), 1600, 1563, 1510, 1447 (C-C Ar); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.10 – 7.94 (2H, m, Ar-H), 7.65 (1H, ddd, *J*=8.4, 6.8, 1.4 Hz, Ar-H), 7.48 (1H, ddd, *J*=8.3, 6.8, 1.3 Hz, Ar-H), 7.17 (1H, s, Ar-H), 3.39 – 3.20 (1H, m, alkyl CH), 2.72 (3H, s, CH_3), 2.08 – 1.80 (5H, m, alkyl CHs), 1.66 – 1.44 (4H, m, alkyl CHs), 1.41 – 1.28 (1H, m, alkyl CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0 (C), 153.4 (C), 148.3 (C), 129.7 (CH), 128.9 (CH), 125.4 (CH), 125.3 (C), 123.0 (CH), 118.5 (CH), 38.9

(CH), 33.7 ($2CH_2$), 27.1 ($2CH_2$), 26.5 (CH_2), 25.7 (CH_3); NMR data matches literature values.[160]

4-Cyclohexyl-6-fluoro-2-methylquinoline (5.3ca)

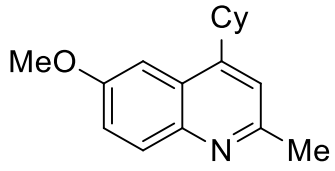


5.3ca

General procedure A was followed, reacting 6-fluoro-2-methylquinoline (24.2 mg, 0.15 mmol), cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and ammonium persulfate (103 mg, 0.45 mmol) in DMSO/H_2O (3 mL/5 µL). The crude product was purified by column chromatography (eluent: 12:1 to 7:1 toluene/EtOAc) to yield product **5.3ca** as a yellow oil (22.8 mg, 0.09 mmol, 62%).

R_F 0.33 (5:1 toluene/EtOAc); ν_{max}/cm^{-1} 2926, 2852 (C-H), 1625, 1604, 1564, 1513, 1465 (C-C Ar); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.00 (1H, dd, *J*=9.2, 5.7 Hz, Ar-H), 7.61 (1H, dd, *J*=10.6, 2.8 Hz, Ar-H), 7.41 (1H, ddd, *J*=9.2, 8.0, 2.8 Hz, Ar-H), 7.17 (1H, s, Ar-H), 3.23 – 3.02 (1H, m, alkyl CH), 2.70 (3H, s, CH_3), 2.03 – 1.79 (5H, m, alkyl CHs), 1.65 – 1.43 (4H, m, alkyl CHs), 1.39 – 1.24 (1H, m, alkyl CH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.2 (d, *J*=245.1 Hz, CF), 158.2 (d, *J*=2.5 Hz, C), 152.9 (d, *J*=5.5 Hz, C), 145.4 (C), 131.9 (d, *J*=9.0 Hz, FCHC<u>H</u>C), 126.0 (d, *J*=9.0 Hz, FCHC<u>C</u>), 119.1 (CH), 118.8 (d, *J*=25.4 Hz, FC<u>C</u>H), 106.7 (d, *J*=22.5 Hz, FC<u>C</u>H), 39.2 (CH), 33.6 ($2CH_2$), 27.0 ($2CH_2$), 26.4 (CH_2), 25.5 (CH_3); Found (TOF MS ASAP+) $[M + H]^+$ 244.1503, $C_{16}H_{19}FN$ requires 244.1503.

4-Cyclohexyl-6-methoxy-2-methylquinoline (5.3da)



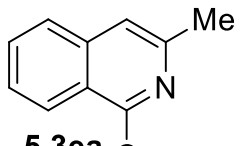
5.3da

General procedure A was followed, reacting 6-methoxy-2-methylquinoline (26.0 mg, 0.15 mmol), cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and ammonium persulfate (103 mg, 0.45 mmol) in DMSO/H_2O (3 mL/5 µL). The crude product was

purified by column chromatography (eluent: 8:1 to 5:1 petrol 40-60 °C/EtOAc) to yield product **5.3da** as a yellow oil (26.0 mg, 0.10 mmol, 68%).

R_F 0.20 (5:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2924, 2850 (C-H), 1598, 1495, 1468 (C-C Ar); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.88 (1H, d, *J*=9.1 Hz, Ar-H), 7.25 (1H, dd, *J*=9.1, 2.7 Hz, Ar-H), 7.20 (1H, d, *J*=2.7 Hz, Ar-H), 7.05 (1H, s, Ar-H), 3.86 (3H, s, OCH_3), 3.20 – 3.01 (1H, m, alkyl CH), 2.60 (3H, s, CH_3), 2.01 – 1.72 (5H, m, alkyl CHs), 1.56 – 1.37 (4H, m, alkyl CHs), 1.33 – 1.21 (1H, m, alkyl CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1 (C), 156.4 (C), 152.1 (C), 144.1 (C), 131.0 (CH), 126.0 (C), 120.4 (CH), 118.7 (CH), 102.1 (CH), 55.6 (CH_3), 39.1 (CH_2), 33.5 ($2CH_2$), 27.0 ($2CH_2$), 26.5 (CH_2), 25.3 (CH_3); Found (FTMS + p NSI) $[M + H]^+$ 256.1696, $C_{17}H_{22}NO$ requires 256.1696.

1-Cyclohexyl-3-methylisoquinoline (5.3ea)

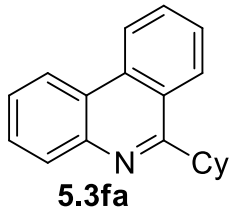


5.3ea

General procedure A was followed, reacting 2-methylisoquinoline (21.5 mg, 0.15 mmol), cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and ammonium persulfate (103 mg, 0.45 mmol) in DMSO/H_2O (3 mL/5 µL). The crude product was purified by column chromatography (eluent: 100:1 petrol 40-60 °C/EtOAc) to yield product **5.3ea** as a colourless oil (30.8 mg, 0.14 mmol, 91%).

R_F 0.35 (50:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2923, 2850 (C-H), 1622, 1592, 1563, 1448 (C-C Ar); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.17 (1H, d, *J*=8.3 Hz, Ar-H), 7.70 (1H, d, *J*=8.0 Hz, Ar-H), 7.58 (1H, ddd, *J*=8.0, 6.8, 1.2 Hz, Ar-H), 7.48 (1H, ddd, *J*=8.3, 6.8, 1.4 Hz, Ar-H), 7.29 (1H, s, Ar-H), 3.53 (1H, tt, *J*=11.2, 3.4 Hz, alkyl CH), 2.67 (3H, s, CH_3), 2.02 – 1.77 (7H, m, alkyl CH), 1.63 – 1.36 (3H, m, alkyl CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1 (C), 150.7 (C), 137.3 (C), 129.4 (CH), 127.1 (CH), 125.8 (CH), 124.8 (CH), 124.5 (C), 116.8 (CH), 41.8 (CH), 32.6 ($2CH_2$), 27.0 ($2CH_2$), 26.3 (CH_2), 24.7 (CH_3); NMR data matches literature values.[178]

6-Cyclohexylphenanthridine (5.3fa)

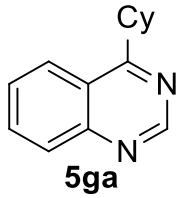


5.3fa

General procedure A was followed, reacting phenanthridine (26.9 mg, 0.15 mmol), cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and ammonium persulfate (103 mg, 0.45 mmol) in DMSO/H_2O (3 mL/5 µL). The crude product was purified by column chromatography (eluent: 1:1 petrol 40-60 ^oC/toluene to 10:1 toluene/Et_2O) to yield product **5.3fa** as a colourless oil (31.8 mg, 0.12 mmol, 80%).

R_F 0.23 (80:1 petrol 40-60 ^oC/Et_2O); ν_{max}/cm^{-1} 2923, 2849 (C-H), 1610, 1581, 1575, 1485 (C-C Ar); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.66 (1H, d, *J*=8.2 Hz, Ar-H), 8.54 (1H, dd, *J*=8.1, 1.5 Hz, Ar-H), 8.32 (1H, d, *J*=8.2 Hz, Ar-H), 8.13 (1H, dd, *J*=8.1, 1.5 Hz, Ar-H), 7.81 (1H, ddd, *J*=8.3, 7.0, 1.3 Hz, Ar-H), 7.75 – 7.65 (2H, m, Ar-H), 7.60 (1H, ddd, *J*=8.3, 7.0, 1.5 Hz, Ar-H), 3.62 (1H, tt, *J*=11.1, 3.3 Hz, alkyl CH), 2.18 – 1.78 (7H, m, alkyl CHs), 1.64 – 1.39 (3H, m, alkyl CHs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4 (C), 144.0 (C), 133.2 (C), 130.09 (CH), 130.05 (CH), 128.5 (CH), 127.2 (CH), 126.3 (CH), 125.8 (CH), 124.9 (C), 123.5 (C), 122.7 (CH), 122.0 (CH), 42.1 (CH), 32.4 ($2CH_2$), 27.0 ($2CH_2$), 26.5 (CH_2); NMR data matches literature values.[160]

4-Cyclohexylquinazoline (5.3ga)

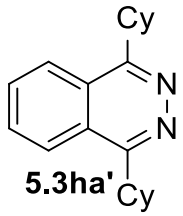


5ga

General procedure B was followed, reacting quinazoline (19.5 mg, 0.15 mmol), cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and ammonium persulfate (103 mg, 0.45 mmol) in DMSO/H_2O (3 mL/5 µL). The crude product was purified by column chromatography (eluent: 10:1 to 8:1 petrol 40-60 ^oC/EtOAc) to yield product **5.3ga** as a colourless oil (24.6 mg, 0.12 mmol, 77%).

R_F 0.20 (10:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2926, 2852 (C-H), 1615, 1569, 1557, 1494 (C-C Ar); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.24 (1H, s, Ar-H), 8.17 (1H, d, *J*=8.4 Hz), 8.03 (1H, d, *J*=8.3 Hz, Ar-H), 7.85 (1H, ddd, *J*=8.4, 6.9, 1.4 Hz, Ar-H), 7.62 (1H, ddd, *J*=8.3, 6.9, 1.3 Hz, Ar-H), 3.55 (1H, tt, *J*=11.5, 3.3 Hz, alkyl CH), 2.00 – 1.72 (7H, m, alkyl CHs), 1.58 – 1.29 (3H, m, alkyl CHs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2 (C), 154.9 (CH), 150.2 (C), 133.4 (CH), 129.5 (CH), 127.4 (CH), 124.3 (CH), 123.4 (C), 41.4 (CH), 32.2 (CH_2), 26.6 (CH_2), 26.1 (CH_2); NMR data matches literature values.[160]

1,4-Dicyclohexylphthalazine (5.3ha')

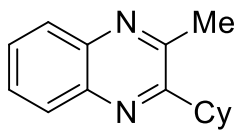


5.3ha'

General procedure B was followed, reacting phthalazine (19.5 mg, 0.15 mmol), cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and ammonium persulfate (206 mg, 0.90 mmol) in DMSO/H_2O (3 mL/5 μL). The crude product was purified by column chromatography (eluent: neat to 15:1 toluene/EtOAc) to yield product **5.3ha'** as a colourless oil (32.5 mg, 0.11 mmol, 74%).

R_F 0.25 (15:1 toluene/EtOAc); ν_{max}/cm^{-1} 2924, 2848 (C-H), 1539, 1446 (C-C Ar); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.21 – 8.08 (2H, m, Ar-H), 7.88 – 7.79 (2H, m, Ar-H), 3.46 (2H, tt, *J*=11.0, 3.9 Hz, alkyl CHs), 2.13 – 1.75 (14H, m, alkyl CHs), 1.61 – 1.30 (6H, m, alkyl CHs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9 (C), 131.2 (CH), 125.1 (C), 124.3 (CH), 40.6 (CH), 32.5 (CH_2), 27.1 (CH_2), 26.4 (CH_2); NMR data matches literature values;[160] m.p. = 133 °C.

2-Cyclohexyl-3-methylquinoxaline (5.3ia)



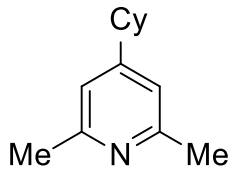
5.3ia

General procedure B was followed, reacting 3-methylquinoxaline (21.6 mg, 0.15 mmol), cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and ammonium persulfate (137 mg, 0.60 mmol) in DMSO/H_2O (3 mL/5 μL). The crude product was purified by

column chromatography (eluent: 50:1 to 30:1 petrol 40-60 °C/EtOAc) to yield product **5.3ia** as a colourless oil (23.5 mg, 0.10 mmol, 69%).

R_F 0.29 (30:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2924, 2851 (C-H), 1565, 1486, 1449 (C-C Ar); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.06 – 7.90 (2H, m, Ar-H), 7.69 – 7.58 (2H, m, Ar-H), 3.03 (1H, tt, *J*=11.5, 3.2 Hz, alkyl CH), 2.78 (3H, s, CH_3), 1.97 – 1.71 (7H, m, alkyl CH), 1.57 – 1.34 (3H, m, alkyl CHs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5 (C), 152.8 (C), 141.5 (C), 140.7 (C), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.3 (CH), 42.7 (CH), 31.7 (CH_2), 26.8 (CH_2), 26.1 (CH_2), 22.8 (CH_3); NMR data matches literature values.[179]

4-Cyclohexyl-2,6-dimethylpyridine (5.3ja)

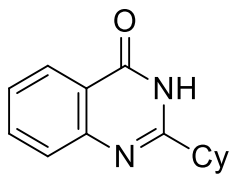


5.3ja

General procedure B was followed, reacting 2,6-lutidine (16.1 mg, 0.15 mmol), cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and ammonium persulfate (103 mg, 0.45 mmol) in DMSO/H_2O (3 mL/5 µL). The crude product was purified by column chromatography (eluent: 1:1 to 1:2 DCM/EtOAc) to yield product **5.3ja** as a yellow oil (14.1 mg, 0.08 mmol, 50%).

R_F 0.26 (1:2 DCM/EtOAc); ν_{max}/cm^{-1} 2924, 2851 (C-H), 1605, 1564, 1447 (C-C Ar); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.79 (2H, s, Ar-H), 2.48 (6H, s, $2CH_3$), 2.47 – 2.33 (1H, m, alkyl CH), 1.90 – 1.71 (5H, m, alkyl CHs), 1.45 – 1.22 (5H, m, alkyl CHs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6 (C), 157.4 (C), 119.1 (CH), 44.0 (CH), 33.7 (CH_2), 26.7 (CH_2), 26.1 (CH_2), 24.5 (CH_3); NMR data matches literature values.[160]

2-Cyclohexylquinazolin-4(3H)-one (5.3ka)

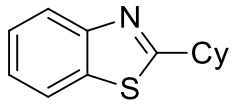


5.3ka

General procedure A was followed, reacting 4-hydroxyquinazoline (21.9 mg, 0.15 mmol), cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and ammonium persulfate (206 mg, 0.90 mmol) in DMSO/H_2O (3 mL/5 µL) for 24 hours. The crude product was purified by column chromatography (eluent: 5:1 to 4:1 petrol 40-60 °C/EtOAc) to yield product **5.3ka** as a colourless oil (19.2 mg, 0.09 mmol, 60%).

R_F 0.28 (3:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 3166 (N-H), 3026, 2929, 2853 (C-H), 1679 (C=O), 1603, 1467 (C-C Ar); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.69 (1H, s, NH), 8.28 (1H, dd, *J*=7.9, 0.9 Hz, Ar-H), 7.86 – 7.65 (2H, m, Ar-H), 7.46 (1H, ddd, *J*=8.1, 6.8, 1.6 Hz, Ar-H), 2.74 (1H, tt, *J*=12.0, 3.4 Hz, alkyl CH), 2.10 – 1.69 (7H, m, alkyl CHs), 1.55 – 1.34 (3H, m, alkyl CHs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3 (C), 160.34 (C), 149.7 (C), 134.8 (CH), 127.5 (CH), 126.4 (CH), 126.3 (CH), 120.9 (C), 45.0 (CH), 30.7 ($2CH_2$), 26.2 ($2CH_2$), 25.9 (CH_2); NMR data matches literature values;[164] m.p. = 133 °C.

2-Cyclohexylbenzo[d]thiazole (5.3la)

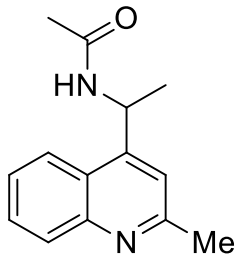


5.3la

General procedure B was followed, reacting benzothiazole (20.3 mg, 0.15 mmol), cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and ammonium persulfate (206 mg, 0.90 mmol) in DMSO/H_2O (3 mL/5 µL) for 40 hours. The crude product was purified by column chromatography (eluent: 80:1 to 60:1 petrol 40-60 °C/EtOAc) to yield product **5.3la** as a colourless oil (8.3 mg, 0.04 mmol, 25%).

R_F 0.36 (30:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2924, 2851 (C-H), 1514, 1448 (C-C Ar); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.97 (1H, ddd, *J*=8.1, 1.2, 0.6 Hz, Ar-H), 7.85 (1H, dm, *J*=7.9 Hz, Ar-H), 7.44 (1H, ddd, *J*=8.3, 7.2, 1.3 Hz, Ar-H), 7.39 – 7.28 (1H, ddd, *J*=7.6, 6.4, 1.2 Hz, Ar-H), 3.11 (1H, tt, *J*=11.6, 3.6 Hz, alkyl CH), 2.26 – 2.15 (2H, m, alkyl CHs), 1.96 – 1.28 (8H, m, alkyl CHs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8 (C), 153.3 (C), 134.7 (C), 125.9 (CH), 124.6 (CH), 122.7 (CH), 121.7 (CH), 43.6 (CH), 33.6 ($2CH_2$), 26.2 ($2CH_2$), 25.9 (CH_2); NMR data matches literature values.[160]

N-(1-(2-methylquinolin-4-yl)ethyl)acetamide (5.3bd)

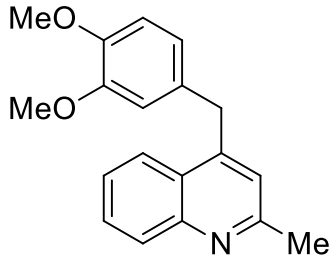


5.3bd

General procedure B was followed, reacting 2-methylquinoline (21.5 mg, 0.15 mmol), acetylalanine (197 mg, 1.50 mmol) and ammonium persulfate (103 mg, 0.45 mmol) in DMSO/H_2O (3 mL/5 µL). The crude product was purified by column chromatography on neutral alumina (eluent: 1:1 petrol 40-60 ^oC/EtOAc to neat EtOAc to 5% MeOH in EtOAc) to yield product **5.3bd** as a yellow oil (31.0 mg, 0.14 mmol, 91%).

R_F 0.42 (EtOAc, neutral alumina plate); ν_{max}/cm^{-1} 3270 (N-H), 3062, 2979, 2932 (C-H), 1651 (C=O), 1602, 1542, 1511 (C-C Ar); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.03 (2H, app. d, *J*=8.9 Hz, Ar-H), 7.68 (1H, ddd, *J*=8.5, 6.9, 1.3 Hz, Ar-H), 7.52 (1H, ddd, *J*=8.2, 6.9, 1.3 Hz, Ar-H), 7.24 (1H, s, Ar-H), 5.87 (1H, app. p, *J*=6.9 Hz, NHC<u>H</u>CH_3), 5.78 (1H, br. s, NH), 2.73 (3H, s, CH_3), 2.03 (3H, s, CH_3), 1.62 (3H, d, *J*=6.7 Hz, CHC<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2 (C), 158.8 (C), 148.4 (C), 148.3 (C), 129.6 (CH), 129.5 (CH), 126.3 (CH), 124.5 (C), 123.2 (CH), 118.0 (CH), 44.5 (CH), 25.7 (CH_3), 23.5 (CH_3), 21.0 (CH_3); Found (FTMS + p NSI) $[M + H]^+$ 229.1334, $C_{14}H_{17}N_2O$ requires 229.1335.

4-(3,4-Dimethoxybenzyl)-2-methylquinoline (5.3bm)



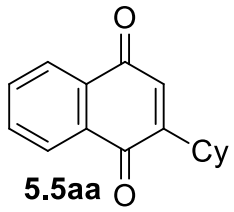
5.3bm

General procedure B was followed, reacting 2-methylquinoline (21.5 mg, 0.15 mmol), 2-(3,4-dimethoxyphenyl)acetic acid (288 mg, 1.50 mmol) and ammonium persulfate (206 mg, 0.90 mmol) in DMSO/H_2O (3 mL/5 µL). The crude product was purified by column chromatography (eluent: 4:1 to 3:1 toluene/EtOAc) and further purified by

column chromatography on neutral alumina (eluent: 6:1 to 1:3 petrol 40-60 °C/EtOAc) to yield product **5.3bm** as a white solid (23.5 mg, 0.08 mmol, 53%).

R_F 0.20 (2:1 petrol 40-60 °C/EtOAc)/0.54 (neutral alumina 3:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 3002, 2934, 2834 (C-H), 1600, 1511, 1463 (C-C Ar); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.03 (1H, dd, *J*=8.3, 1.5 Hz, Ar-H), 7.98 (2H, dd, *J*=8.4, 1.3Hz, Ar-H), 7.66 (1H, ddd, *J*=8.4, 6.9, 1.5 Hz, Ar-H), 7.46 (1H, ddd, *J*=8.3, 6.9, 1.3 Hz, Ar-H), 7.00 (1H, s, Ar-H), 6.81 (1H, d, *J*=8.0 Hz, Ar-H), 6.72 (1H, s, Ar-H), 6.71 (H, d, *J*=8.0 Hz, Ar-H), 4.35 (2H, s, CH_2), 3.86 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 2.68 (3H, s, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0 (C), 149.4 (C), 148.3 (C), 148.0 (C), 146.9 (C), 131.4 (C), 129.6 (CH), 129.2 (CH), 126.1 (C), 125.8 (CH), 123.7 (CH), 122.6 (CH), 121.3 (CH), 112.6 (CH), 111.7 (CH), 56.10 (CH_3), 56.08 (CH_3), 37.8 (CH_2), 25.5 (CH_3); Found (FTMS + p NSI) $[M + H]^+$ 294.1487, $C_{19}H_{20}NO_2$ requires 294.1489; m.p. = 109 °C.

2-Cyclohexylnaphthalene-1,4-dione (5.5aa)

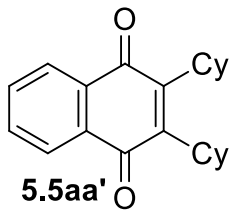


5.5aa

General procedure A was followed, reacting 1,4-naphthaquinone (23.7 mg, 0.15 mmol), cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and ammonium persulfate (68.5 mg, 0.30 mmol) in DMSO/H_2O (3 mL/5 µL). The crude product was purified by column chromatography (eluent: 1:1 to 1:2 petrol 40-60 °C/toluene) to yield product **5.5aa** as a yellow paste (25.1 mg, 0.11 mmol, 70%).

R_F 0.41 (30:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2918, 2851 (C-H), 1654, 1656 (C=O), 1593, 1450 (C-C Ar); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.14 – 7.87 (2H, m, Ar-H), 7.71 – 7.58 (2H, m, Ar-H), 6.66 (1H, d, *J*=1.1 Hz, =CH), 2.92 – 2.74 (1H, m, alkyl CH), 1.82 – 1.73 (4H, m, alkyl CHs), 1.46 – 1.29 (2H, m, alkyl CHs), 1.25 – 1.09 (4H, m, alkyl CHs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.7 (C), 184.9 (C), 156.4 (C), 133.71 (CH), 133.68 (CH), 133.2 (CH), 132.6 (C), 132.1 (C), 126.8 (CH), 126.0 (CH), 36.8 (CH), 32.4 ($2CH_2$), 26.5 ($2CH_2$), 26.2 (CH_2); NMR data matches literature values.[180]

2,3-Dicyclohexylnaphthalene-1,4-dione (5.5aa')

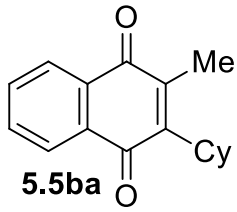


5.5aa'

General procedure A was followed, reacting 1,4-naphthaquinone (23.7 mg, 0.15 mmol), cyclohexanecarboxylic acid (384 mg, 3.00 mmol) and ammonium persulfate (137 mg, 0.60 mmol) in DMSO/H_2O (3 mL/5 µL) for 3 days. The crude product was purified by column chromatography (eluent: 2:1 petrol 40-60 ^oC/toluene) to yield product **5.5aa'** as a yellow solid (31.1 mg, 0.10 mmol, 64%).

R_F 0.46 (50:1 petrol 40-60 ^oC/EtOAc); ν_{max}/cm^{-1} 2923, 2851 (C-H), 1654 (C=O), 1614, 1592, 1443 (C-C Ar); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.03 – 7.94 (2H, m, Ar-H), 7.70 – 7.58 (2H, m, Ar-H), 3.15 – 2.99 (2H, m, alkyl CHs), 2.13 – 1.19 (4H, m, alkyl CHs)), 1.91 – 1.72 (6H, m, alkyl CHs)), 1.60 (4H, m, alkyl CHs)), 1.40 – 1.32 (6H, m, alkyl CHs)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.0 (C), 151.0 (C), 133.2 (CH), 132.6 (C), 126.0 (CH), 39.9 (CH), 30.7 ($2CH_2$), 27.2 ($2CH_2$), 26.1 (CH_2); Found (TOF MS ASAP+) $[M + H]^+$ 323.2011, $C_{22}H_{27}O_2$ requires 323.2011; m.p. = 107 ^oC.

2-Cyclohexyl-3-methylnaphthalene-1,4-dione (5.5ba)



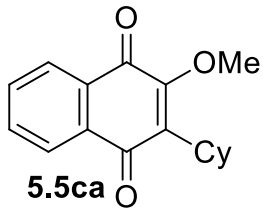
5.5ba

General procedure A was followed, reacting menadione (25.8 mg, 0.15 mmol), cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and ammonium persulfate (68.5 mg, 0.30 mmol) in DMSO/H_2O (3 mL/5 µL). The crude product was purified by column chromatography (eluent: 2:1 to 1:1 petrol 40-60 ^oC/toluene) to yield product **5.5ba** as a yellow solid (27.4 mg, 0.11 mmol, 72%).

R_F 0.44 (50:1 petrol 40-60 ^oC/EtOAc); ν_{max}/cm^{-1} 2933, 2849 (C-H), 1655 (C=O), 1592, 1454 (C-C Ar); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.13 – 7.90 (2H, m, Ar-H), 7.73 – 7.57 (2H, m, Ar-H), 2.87 (1H, tt, *J*=12.1, 3.4 Hz, alkyl CH), 2.22 (3H, s, alkyl CHs)), 2.16 – 1.95 (2H,

m, alkyl CHs)), 1.94 – 1.68 (3H, m, alkyl CHs)), 1.68 – 1.51 (2H, m, alkyl CHs)), 1.45 – 1.14 (3H, m, alkyl CHs)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.8 (C), 185.3 (C), 150.7 (C), 143.2 (C), 133.5 (CH), 133.2 (CH), 132.9 (C), 131.9 (C), 126.3 (CH), 126.1 (CH), 40.9 (CH), 30.0 ($2CH_2$), 27.1 ($2CH_2$), 26.1 (CH_2), 12.7 (CH_3); NMR data matches literature values;[181] m.p. = 78 °C (lit.[181] 77.5-79.0 °C).

2-Cyclohexyl-3-methoxynaphthalene-1,4-dione (5.5ca)

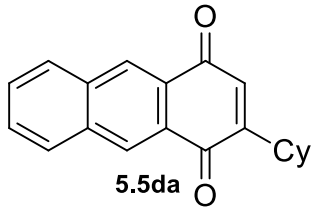


5.5ca

General procedure A was followed, reacting 1,4-naphthaquinone (28.2 mg, 0.15 mmol), cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and ammonium persulfate (68.5 mg, 0.30 mmol) in DMSO/H_2O (3 mL/5 μL). The crude product was purified by column chromatography (eluent: 2:1 to 1:1 petrol 40-60 °C/toluene) to yield product **5.5ca** as a yellow paste (22.2 mg, 0.08 mmol, 55%).

R_F 0.26 (40:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2924, 2851 (C-H), 1667, 1651 (C=O), 1594, 1577, 1448 (C-C Ar); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09 – 7.97 (2H, m, Ar-H), 7.74 – 7.61 (2H, m, Ar-H), 4.06 (3H, s, CH_3), 3.09 (1H, tt, *J*=12.1, 3.3 Hz, alkyl CH), 1.99 – 1.67 (5H, m, alkyl CHs)), 1.65 – 1.53 (2H, m, alkyl CHs)), 1.45 – 1.22 (3H, m, alkyl CHs)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.7 (C), 182.1 (C), 158.5 (C), 139.9 (C), 133.9 (CH), 133.2 (CH), 132.4 (C), 131.6 (C), 126.5 (CH), 126.0 (CH), 61.4 (CH_3), 36.0 (CH), 30.1 ($2CH_2$), 27.0 ($2CH_2$), 26.1 (CH_2); Found (TOF MS ASAP+) $[M + H]^+$ 271.1339, $C_{17}H_{19}O_3$ requires 271.1334.

2-Cyclohexylanthracene-1,4-dione (5.5da)



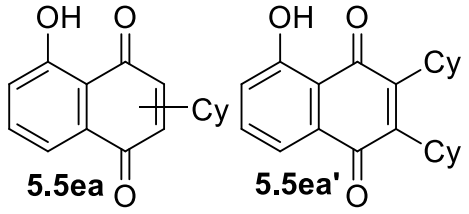
5.5da

General procedure A was followed, reacting 1,4-anthraquinone (31.2 mg, 0.15 mmol), cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and ammonium persulfate (68.5 mg,

0.30 mmol) in DMSO/H_2O (3 mL/5 µL). The crude product was purified by column chromatography (eluent: 100:1 to 60:1 petrol 40-60 °C/EtOAc) to yield product **5.5da** as a yellow solid (33.9 mg, 0.12 mmol, 78%).

R_F 0.24 (50:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2957, 2919, 2846 (C-H), 1660 (C=O), 1615, 1588, 1459 (C-C Ar); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.58 (1H, s, Ar-H), 8.54 (1H, s, Ar-H), 8.06 – 7.98 (2H, m, Ar-H), 7.70 – 7.59 (2H, m, Ar-H), 6.82 (1H, s, =CH), 2.96 (1H, td, *J*=11.8, 2.6 Hz, alkyl CH), 1.95 – 1.73 (5H, m, alkyl CHs)), 1.57 – 1.37 (2H, m, alkyl CHs)), 1.35 – 1.15 (3H, m, alkyl CHs)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.3 (C), 184.5 (C), 157.9 (C), 135.0 (C), 134.8 (C), 134.7 (CH), 130.24 (CH), 130.20 (CH), 129.43 (CH), 129.39 (CH), 129.2 (CH), 129.1 (C), 128.7 (C), 128.2 (CH), 37.0 (CH), 32.4 ($2CH_2$), 26.6 ($2CH_2$), 26.2 (CH_2); Found (FTMS + p NSI) $[M + H]^+$ 291.1388, $C_{20}H_{19}O_2$ requires 291.1385; m.p. = 185 °C.

2-Cyclohexyl-5-hydroxynaphthalene-1,4-dione + 2-cyclohexyl-8-hydroxynaphthalene-1,4-dione (5.5ea) + 2,3-Dicyclohexyl-5-hydroxynaphthalene-1,4-dione (5.5ea')



General procedure A was followed, reacting 5-hydroxy-1,4-naphthalenedione (26.1 mg, 0.15 mmol), cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and ammonium persulfate (68.5 mg, 0.30 mmol) in DMSO/H_2O (3 mL/5 µL). The crude product was purified by column chromatography (eluent: 5:1 to neat petrol 40-60 °C/toluene) to yield isomeric products **5.5ea** (1.3:1 ratio) and product **5.5ea'** as a yellow solids.

5.5ea$_{major}$ (14.0 mg, 0.05 mmol, 36%).

R_F 0.46 (50:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2921, 2854 (C-H), 1633 (C=O) 1654, 1593, 1579, 1456 (C-C Ar); ^1H NMR ($CDCl_3$, 300 MHz) δ 11.98 (1H, s, OH), 7.71 – 7.50 (2H, m, Ar-H), 7.23 (1H, dd, *J*=7.6, 2.0 Hz, Ar-H), 6.69 (1H, d, *J*=1.0 Hz, =CH), 2.96 – 2.82 (1H, m, alkyl CH), 1.91 – 1.71 (5H, m, alkyl CHs)), 1.54 – 1.35 (2H, m, alkyl CHs)), 1.31 – 1.15 (3H, m, alkyl CHs)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.0 (C), 184.2 (C), 161.2 (C), 157.9 (C), 136.2 (CH), 133.0 (CH), 132.6 (C), 124.1 (CH), 119.5 (CH), 115.0 (C), 37.0 (CH),

32.5 ($2CH_2$), 26.5 ($2CH_2$), 26.2 (CH_2); Found (TOF MS ASAP+) $[M + H]^+$ 257.1179, $C_{16}H_{17}O_3$ requires 257.1178; m.p. = 112 °C.

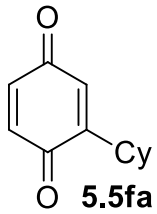
5.5ea$_{minor}$ (10.6 mg, 0.04 mmol, 28%).

R_F 0.38 (50:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2953, 2927, 2848 (C-H), 1636 (C=O) 1666, 1603, 1451 (C-C Ar); ^1H NMR ($CDCl_3$, 300 MHz) δ 12.16 (1H, s, OH), 7.64 – 7.56 (2H, m, Ar-H), 7.28 – 7.19 (1H, m, Ar-H), 6.71 (1H, d, *J*=1.1 Hz, =CH), 3.03 – 2.76 (1H, m, alkyl CH), 1.93 – 1.74 (5H, m, alkyl CHs)), 1.54 – 1.36 (2H, m, alkyl CHs)), 1.32 – 1.18 (3H, m, alkyl CHs)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.4 (C), 185.0 (C), 161.8 (C), 156.3 (C), 136.4 (CH), 134.1 (CH), 132.1 (C), 124.3 (CH), 118.7 (CH), 115.5 (C), 36.4 (CH), 32.4 ($2CH_2$), 26.5 ($2CH_2$), 26.1 (CH_2); Found (TOF MS ASAP+) $[M + H]^+$ 257.1181, $C_{16}H_{17}O_3$ requires 257.1178; m.p. = 112 °C.

5.5ea' (5.1 mg, 0.02 mmol, 10%)

R_F 0.68 (50:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2931, 2915, 2850 (C-H), 1633 (C=O) 1661, 1608, 1575, 1458 (C-C Ar); ^1H NMR ($CDCl_3$, 300 MHz) δ 12.27 (1H, s, OH), 7.57 – 7.50 (2H, m, Ar-H), 7.21 – 7.14 (1H, m, Ar-H), 3.19 – 2.94 (2H, m, alkyl CHs), 2.15 – 1.56 (14H, m, alkyl CHs)), 1.45 – 1.26 (6H, m, alkyl CHs)); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.5 (C), 185.4 (C), 161.2 (C), 152.6 (C), 150.7 (C), 135.8 (C), 132.9 (CH), 123.5 (CH), 118.6 (CH), 115.5 (C), 40.14 (CH), 40.11 (CH), 30.75 (CH_2), 30.72 (CH_2), 27.3 (CH_2), 27.2 (CH_2), 26.12 (CH_2), 26.10 (CH_2); Found (TOF MS ASAP+) $[M + H]^+$ 339.1954, $C_{22}H_{27}O_3$ requires 339.1960; m.p. = 153 °C.

[1,1'-bi(cyclohexane)]-3,6-diene-2,5-dione (5.5fa)

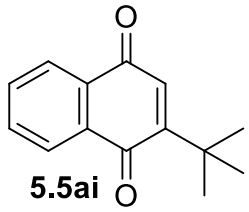


5.5fa

General procedure A was followed, reacting 1,4-benzoquinone (16.2 mg, 0.15 mmol), cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and ammonium persulfate (68.5 mg, 0.30 mmol) in DMSO/H_2O (3 mL/5 μL). The crude product was purified by column chromatography (eluent: 2:1 to 1:2 petrol 40-60 °C/toluene) to yield product **5.5fa** as a yellow paste (7.7 mg, 0.04 mmol, 27%).

R_F 0.37 (20:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2938, 2851 (C-H), 1645 (C=O), 1593, 1447 (C-C Ar); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.75 (1H, d, *J*=10.1 Hz, Ar-H), 6.69 (1H, dd, *J*=10.1, 2.3 Hz, Ar-H), 6.50 (1H, dd, *J*=2.3, 1.1 Hz, Ar-H), 2.75 – 2.62 (1H, m, alkyl CH), 1.87 – 1.70 (5H, m, alkyl CHs), 1.47 – 1.31 (2H, m, alkyl CHs), 1.28 – 1.10 (3H, m, alkyl CHs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.4 (C), 187.3 (C), 154.2 (C), 137.2 (CH), 136.1 (CH), 130.9 (CH), 36.5 (CH), 32.2 ($2CH_2$), 26.4 ($2CH_2$), 26.1 (CH_2); NMR data matches literature values.[181]

2-(*tert*-Butyl)naphthalene-1,4-dione (5.5ai)

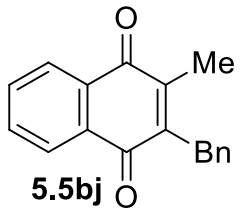


5.5ai

General procedure A was followed, reacting 1,4-naphthaquinone (23.7 mg, 0.15 mmol), pivalic acid (153 mg, 1.50 mmol) and ammonium persulfate (68.5 mg, 0.30 mmol) in DMSO/H_2O (3 mL/5 µL). The crude product was purified by column chromatography (eluent: 100:1 to 80:1 petrol 40-60 °C/EtOAc) to yield product **5.5ai** as a yellow solid (21.4 mg, 0.10 mmol, 67%).

R_F 0.21 (60:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2969, 2959, 2872 (C-H), 1664, 1654 (C=O), 1601, 1592, 1483 (C-C Ar); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.13 – 7.98 (2H, m, Ar-H), 7.78 – 7.63 (2H, m, Ar-H), 6.84 (1H, s, =CH), 1.37 (9H, s, $3CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.1 (C), 185.1 (C), 158.5 (C), 134.0 (CH), 133.9 (CH), 133.7 (C), 133.4 (CH), 131.7 (C), 127.0 (CH), 125.7 (CH), 35.9 (C), 29.5 ($3CH_3$); NMR data matches literature values;[182] m.p. = 74-76 °C (lit.[182] 75-76 °C).

2-Benzyl-3-methylnaphthalene-1,4-dione (5.5bj)

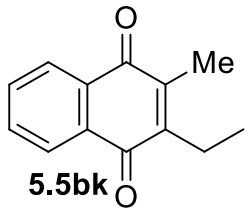


5.5bj

General procedure A was followed, reacting menadione (25.8 mg, 0.15 mmol), 2-phenylacetic acid (204 mg, 1.50 mmol) and ammonium persulfate (68.5 mg, 0.30 mmol) in DMSO/H_2O (3 mL/5 µL). The crude product was purified by column chromatography (eluent: 100:1 to 60:1 petrol 40-60 °C/EtOAc) to yield product **5.5bj** as a yellow solid (33.5 mg, 0.13 mmol, 85%).

R_F 0.21 (60:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 3063, 3025, 2963, 2934 (C-H), 1660, 1652 (C=O), 1619, 1590, 1494 (C-C Ar); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.14 – 8.05 (2H, m, Ar-H), 7.75 – 7.66 (2H, m, Ar-H), 7.37 – 7.07 (5H, m, Ar-H), 4.05 (2H, s, CH_2), 2.26 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.5 (C), 184.8 (C), 145.4 (C), 144.5 (C), 138.2 (C), 133.60 (CH), 133.56 (CH), 132.23 (C), 132.15 (C), 128.8 (CH), 128.7 (CH), 126.6 (CH), 126.5 (CH), 126.4 (CH), 32.5 (CH_2), 13.4 (CH_3); NMR data matches literature values;[183] m.p. = 106 °C (lit.[183] 106-108 °C).

2-Ethyl-3-methylnaphthalene-1,4-dione (5.5bk)

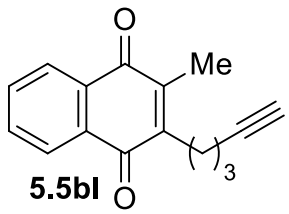


5.5bk

General procedure A was followed, reacting menadione (25.8 mg, 0.15 mmol), propionic acid (112 µL, 1.50 mmol) and ammonium persulfate (68.5 mg, 0.30 mmol) in DMSO/H_2O (3 mL/5 µL). The crude product was purified by column chromatography (eluent: 50:1 petrol 40-60 °C/EtOAc) to yield product **5.5bk** as a yellow paste (18.9 mg, 0.09 mmol, 63%).

R_F 0.25 (60:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2968, 2934, 2873 (C-H), 1657, 1652 (C=O), 1616, 1594, 1582, 1459 (C-C Ar); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.12 – 8.02 (2H, m, Ar-H), 7.72 – 7.63 (2H, m, Ar-H), 2.66 (2H, q, *J*=7.5 Hz, CH_2), 2.19 (3H, s, =CCH_3), 1.12 (3H, t, *J*=7.5 Hz, $CH_2C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.7 (C), 184.7 (C), 148.7 (C), 143.0 (C), 133.5 (CH), 133.4 (CH), 132.4 (C), 132.3 (C), 126.4 (CH), 126.3 (CH), 20.5, 13.0, 12.5; NMR data matches literature values;[184] m.p. = 66 °C (lit.[184] 66-68 °C).

2-Methyl-3-(pent-4-yn-1-yl)naphthalene-1,4-dione (5.5bl)

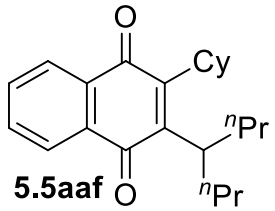


5.5bl

General procedure A was followed, reacting menadione (25.8 mg, 0.15 mmol), 5-hexynoic acid (166 µL, 1.50 mmol) and ammonium persulfate (68.5 mg, 0.30 mmol) in DMSO/H_2O (3 mL/5 µL). The crude product was purified by column chromatography (eluent: 1:1 to neat petrol 40-60 ^oC/toluene) to yield product **5.5bl** as a yellow solid (21.0 mg, 0.09 mmol, 59%).

R_F 0.26 (30:1 petrol 40-60 ^oC/EtOAc); ν_{max}/cm^{-1} 3278 (H-C alkyne), 2961, 2937, 2867 (C-H), 1655 (C=O), 1619, 1594, 1457 (C-C Ar); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.12 – 8.04 (2H, m, Ar-H), 7.73 – 7.65 (2H, m, Ar-H), 2.83 – 2.72 (2H, m, $=CCH_2$), 2.31 (2H, td, *J*=6.9, 2.6 Hz, $CH_2C\equiv$), 2.23 (3H, s, CH_3), 2.00 (1H, t, *J*=2.6 Hz, ≡CH), 1.80 – 1.66 (2H, m, $CH_2C\underline{H}_2CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.4 (C), 184.8 (C), 146.6 (C), 143.9 (C), 133.6 (CH), 133.5 (CH), 132.3 (2 overlapping Cs), 126.5 (CH), 126.4 (CH), 83.9 (C), 69.2 (CH), 27.6 (CH_2), 26.3 (CH_2), 18.9 (CH_2), 12.8 (CH_3); Found (FTMS + p NSI) $[M + H]^+$ 239.1077, $C_{16}H_{15}O_2$ requires 239.1072; m.p. = 98 ^oC.

2-Cyclohexyl-3-(heptan-4-yl)naphthalene-1,4-dione (5.5aaf)



5.5aaf

To a backfilled Schlenk tube 1,4-naphthoquinone (23.7 mg, 0.15 mmol), cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and ammonium persulfate (68.5 mg, 0.30 mmol) were added. After a final backfill DMSO/water (3mL/5 µL degassed by bubbling with argon (2 balloons/15 mins)) was added and the reaction was sealed and stirred overnight at 40 ^oC.

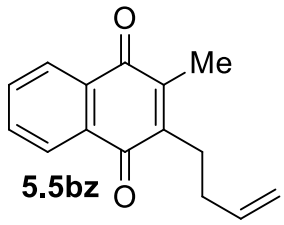
The reaction mixture was diluted with DCM (15 mL) and washed twice with sat. $NaHCO_3$ solution. The aqueous layer was then extracted with DCM (2 x 15 mL) and the combined organic layers were washed with brine (40 mL), dried (Na_2SO_4) and

concentrated before being transferred to a backfilled Schlenk tube with DMSO/water (3 mL/5 µL, degassed by bubbling with argon). After 5 minutes of bubbling with argon, 2-propylpentanoic acid (238 µL, 1.50 mmol) and ammonium persulfate (68.5 mg, 0.30 mmol) were added, and the reaction was sealed and stirred overnight at 40 °C.

The reaction mixture was diluted with DCM (15 mL) and washed with sat. $NaHCO_3$ solution. The aqueous layer was then extracted with DCM (2 x 15 mL) and the combined organic layers were washed with brine (40 mL), dried (Na_2SO_4) and concentrated to give the crude product. The crude product was purified by column chromatography (eluent: 5:1 to 3:1 petrol 40-60 °C/toluene) to yield product **5.5aaf** as a yellow paste (23.2 mg, 0.07 mmol, 46%).

R_F 0.56 (50:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2956, 2924, 2855 (C-H), 1657 (C=O), 1594, 1451 (C-C Ar); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.05 – 7.94 (2H, m, Ar-H), 7.70 – 7.60 (2H, m, Ar-H), 2.92 (1H, tt, *J*=12.0, 3.3 Hz, C<u>H</u>Cy), 2.24 – 2.07 (2H, m, alkyl CHs), 1.90 – 1.52 (9H, m, alkyl CHs), 1.47 – 1.08 (8H, m, alkyl CHs), 0.88 (6H, t, *J*=7.3 Hz, $2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.8 (C), 185.6 (C), 150.02 (C), 150.00 (C), 133.2 (CH), 133.1 (CH), 133.0 (C), 126.1 (C), 126.0 (2CH), 41.21 (CH), 41.19 (CH), 37.0 (CH_2), 30.7 (CH_2), 27.3 (CH_2), 26.1 (CH_2), 22.0 (CH_2), 14.5 (CH_3); Found (TOF MS ASAP+) $[M + H]^+$ 339.2322, $C_{23}H_{31}O_2$ requires 339.2324.

2-(But-3-en-1-yl)-3-methylnaphthalene-1,4-dione (5.5bz)

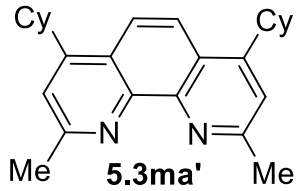


5.5bz

General procedure A was followed, reacting menadione (25.8 mg, 0.15 mmol), cyclopropylacetic acid (140 µL, 1.50 mmol) and ammonium persulfate (68.5 mg, 0.30 mmol) in DMSO/H_2O (3 mL/5 µL). The crude product was purified by column chromatography (eluent: 1:1 petrol 40-60 °C/toluene) to yield product **5.5bz** as a yellow paste (9.9 mg, 0.04 mmol, 29%).

R_F 0.19 (1:1 petrol 40-60 °C/toluene); ν_{max}/cm^{-1} 3074, 3017, 2925 (C-H), 1656 (C=O), 1617, 1595 (C-C Ar); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.14 – 7.98 (2H, m, Ar-H), 7.74 – 7.57 (2H, m, Ar-H), 5.87 (1H, ddt, *J*=16.9, 10.1, 6.8 Hz, $CH_2\underline{H}C$=), 5.05 (1H, app. dq, *J*=16.9, 1.6 Hz, =C$\underline{H}_2$), 4.99 (1H, ddt, *J*=10.1, 2.0, 1.2 Hz, =C$\underline{H}_2$), 2.74 (1H, t, *J*=7.1 Hz, C$\underline{H}_2CH_2$), 2.25 (2H, app. qm, *J*=7.1 Hz, C$\underline{H}_2$HC=), 2.19 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.4 (C), 184.7 (C), 146.6 (C), 143.8 (C), 137.4 (CH), 133.52 (CH), 133.48 (CH), 132.3 (2C), 126.44 (CH), 126.37 (CH), 115.7 (CH_2), 32.8 (CH_2), 26.8 (CH_2), 13.0 (CH_3); Found (TOF MS ASAP+) $[M + H]^+$ 227.1076, $C_{15}H_{15}O_2$ requires 227.1072.

4,7-Dicyclohexyl-2,9-dimethyl-1,10-phenanthroline (5.3ma')

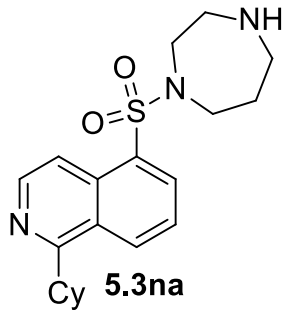


5.3ma'

General procedure A was followed, reacting neocuproine (32.6 mg, 0.15 mmol), cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and ammonium persulfate (103 mg, 0.45 mmol) in DMSO/H_2O (3 mL/5 µL). The crude product was purified by column chromatography (eluent: EtOAc) to yield product **5.3ma'** as a white solid (46.9 mg, 0.12 mmol, 82%).

R_F 0.21 (EtOAc); ν_{max}/cm^{-1} 2926, 2850 (C-H), 1621, 1582, 1549, 1444 (C-C Ar); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.99 (2H, s, Ar-H), 7.33 (2H, s, Ar-H), 3.41 – 3.23 (2H, m, alkyl CH), 2.88 (6H, s, alkyl CHs), 2.07 – 1.81 (10H, m, alkyl CHs), 1.64 – 1.47 (8H, m, alkyl CHs), 1.42 – 1.27 (2H, m, alkyl CHs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9 (C), 153.0 (C), 146.1 (C), 124.5 (C), 120.3 (CH), 119.8 (CH), 39.2 (CH_2), 33.7 (CH_2), 27.0 (CH_2), 26.4 (CH_2), 26.2 (CH_3); Found (FTMS + p NSI) $[M + H]^+$ 373.2637, $C_{26}H_{33}N_2$ requires 373.2638; m.p. = 114 °C.

5-((1,4-Diazepan-1-yl)sulfonyl)-1-cyclohexylisoquinoline (5.3na)

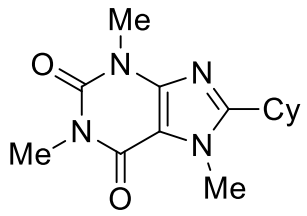


5.3na

General procedure A was followed, reacting Fasudil.HCl (24.6 mg, 0.08 mmol), cyclohexanecarboxylic acid (192 mg, 0.75 mmol) and ammonium persulfate (68.5 mg, 0.30 mmol) in DMSO/H_2O (1.5 mL/3 µL). The crude product was purified by column chromatography (eluent: 1 to 10% MeOH/DCM + 0.1% Et_3N) and further purified by column chromatography on neutral alumina (eluent: 1 to 20% MeOH/DCM) to yield impure product **5.3na** as a yellow oil (12.3 mg, 0.03 mmol, 44%, 90% purity).

R_F 0.14 (5% MeOH/DCM + 0.1% Et_3N)/0.38 (neutral alumina 2% MeOH/DCM); ν_{max}/cm^{-1} 3019, 2929, 2853 (C-H), 1610, 1580, 1558, 1490, 1450 (C-C Ar); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.62 (1H, d, *J*=6.1 Hz, Ar-H), 8.47 (1H, d, *J*=8.8 Hz, Ar-H), 8.30 (1H, dd, *J*=7.4, 1.1 Hz, Ar-H), 8.25 (1H, dd, *J*=6.1, 0.8 Hz, Ar-H), 7.64 (1H, dd, *J*=8.5, 7.4 Hz, Ar-H), 3.56 (1H, tt, *J*=11.4, 3.2 Hz, alkyl CH), 3.54 – 3.42 (4H, m, NCH_2), 3.21 (1H, br. s, NH), 3.09 – 2.97 (4H, m, NCH_2), 2.00 – 1.76 (9H, m, NCH_2 + alkyl CHs), 1.60 – 1.35 (3H, m, alkyl CHs); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8 (C), 144.1 (CH), 135.4 (C), 132.5 (C), 132.4 (CH), 130.5 (CH), 127.1 (C), 125.2 (CH), 115.6 (CH), 50.4 (CH_2), 50.3 (CH_2), 47.5 (CH_2), 47.4 (CH_2), 42.3 (CH), 32.9 (CH_2), 30.6 (CH_2), 30.0 (CH_2), 26.3 (CH_2); NMR data matches literature values.[164]

8-Cyclohexyl-1,3,7-trimethyl-1H-purine-2,6(3H,7H)-dione (5.3oa)



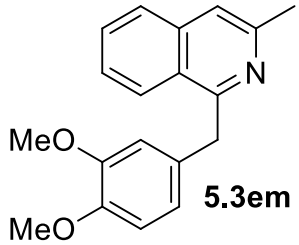
5.3oa

General procedure A was followed, reacting caffeine (29.1 mg, 0.15 mmol), cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and ammonium persulfate (103 mg,

0.45 mmol) in DMSO/H_2O (3 mL/5 µL) for 40h. The crude product was purified by column chromatography (eluent: 3:1 to 2:1 petrol 40-60 °C/EtOAc) to yield product **5.3oa** as a white powder (11.6 mg, 0.04 mmol, 28%).

R_F 0.30 (2:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 2924, 2841 (C-H), 1695, 1663 (C=O), 1651, 1603, 1541, 1493 (C-C Ar); ^1H NMR ($CDCl_3$, 300 MHz) δ 3.92 (3H, s, CH_3), 3.56 (3H, s, CH_3), 3.39 (3H, s, CH_3), 2.70 (1H, tt, *J*=11.5, 3.4 Hz, alkyl CH), 1.93 – 1.61 (7H, m, alkyl CHs), 1.47 – 1.27 (3H, m, alkyl CHs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1 (C), 155.6 (C), 151.9 (C), 148.3 (C), 107.2 (C), 35.9 (CH), 31.5 (CH_3), 31.1 (CH_2), 29.9 (CH_3), 28.0 (CH_3), 26.1 (CH_2), 25.7 (CH_2); NMR data matches literature values;[159] m.p. = 210 °C (lit.[185] 212 °C).

1-(3,4-Dimethoxybenzyl)-3-methylisoquinoline (5.3em)

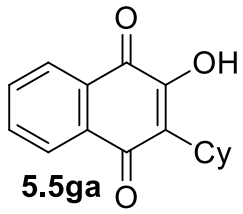


5.3em

General procedure A was followed, reacting 3-methylisoquinoline (21.5 mg, 0.15 mmol), 2-(3,4-dimethoxyphenyl)acetic acid (288 mg, 1.50 mmol) and ammonium persulfate (137 mg, 0.45 mmol) in DMSO/H_2O (3 mL/5 µL). The crude product was purified by column chromatography (eluent: 4:1 to 2:1 petrol 40-60 °C/EtOAc) to yield product **5.3em** as a yellow oil (38.0 mg, 0.13 mmol, 86%).

R_F 0.48 (2:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 3013, 2934, 2834 (C-H), 1626, 1590, 1512, 1463 (C-C Ar); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.09 (1H, d, *J*=8.3 Ar-H), 7.69 (1H, d, *J*=8.2 Hz, Ar-H), 7.55 (1H, ddd, *J*=8.2, 6.8, 1.2 Hz, Ar-H), 7.41 (1H, ddd, *J*=8.3, 6.8, 1.3 Hz, Ar-H), 7.38 (1H, s, Ar-H), 6.86 (1H, d, *J*=1.8 Hz, Ar-H), 6.76 (1H, dd, *J*=8.2, 1.8 Hz, Ar-H), 6.71 (1H, d, *J*=8.2 Hz, Ar-H), 4.58 (2H, s, CH_2), 3.79 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 2.71 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8 (C), 150.5 (C), 148.9 (C), 147.5 (C), 137.5 (C), 132.3 (C), 129.9 (CH), 126.8 (CH), 126.3 (CH), 125.9 (CH), 125.4 (C), 120.6 (CH), 118.0 (CH), 112.0 (CH), 111.2 (CH), 55.9 ($2CH_3$), 41.7 (CH_2), 24.4 (CH_3); Found (FTMS + p NSI) $[M + H]^+$ 294.1487, $C_{19}H_{20}NO_2$ requires 294.1489.

2-Cyclohexyl-3-hydroxynaphthalene-1,4-dione (5.5ga)

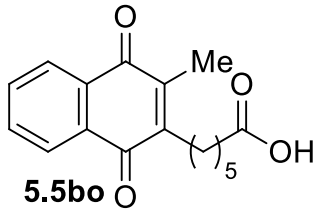


5.5ga

General procedure A was followed, reacting 2-hydroxy-1,4-naphthoquinone (26.1 mg, 0.15 mmol), cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and ammonium persulfate (68.5 mg, 0.30 mmol) in DMSO/H_2O (3 mL/5 µL). The crude product was purified by column chromatography (eluent: 1:1 to neat petrol 40-60 °C/toluene) to yield product **5.5ga** as an orange solid (12.5 mg, 0.05 mmol, 33%).

R_F 0.40 (30:1 petrol 40-60 °C/EtOAc); ν_{max}/cm^{-1} 3348 (H-O), 2926, 2918, 2850 (C-H), 1656, 1646 (C=O), 1633, 1590, 1453 (C-C Ar); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (1H, dd, *J*=7.8, 1.1 Hz, Ar-H), 8.05 (1H, dd, *J*=7.6, 1.3 Hz, Ar-H), 7.74 (1H, td, *J*=7.6, 1.5 Hz, Ar-H), 7.66 (1H, td, *J*=7.5, 1.4 Hz, Ar-H), 7.44 (1H, s, OH), 3.07 (1H, tt, *J*=12.2, 3.5 Hz, alkyl CH), 2.06 – 1.89 (2H, m, alkyl CHs)), 1.85 – 1.58 (5H, m, alkyl CHs)), 1.45 – 1.25 (3H, m, alkyl CHs)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.7 (C), 182.1 (C), 153.0 (C), 135.0 (CH), 133.3 (C), 133.0 (CH), 129.4 (C), 128.0 (C), 127.1 (CH), 126.1 (CH), 35.3 (CH), 29.4 ($2CH_2$), 27.0 ($2CH_2$), 26.1 (CH_2); NMR data matches literature values;[186] m.p. = 133 °C (lit. [186] 133-135° C).

6-(3-Methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)hexanoic acid (5.5bo)



5.5bo

General procedure A was followed, reacting menadione (25.8 mg, 0.15 mmol), pimelic acid (192 mg, 1.50 mmol) and ammonium persulfate (68.5 mg, 0.30 mmol) in DMSO/H_2O (3 mL/5 µL). The crude product was purified by column chromatography (eluent: 6:1 to 4:1 petrol 40-60 °C/EtOAc + 0.5% AcOH) to yield product **5.5bo** as a yellow solid (26.1 mg, 0.09 mmol, 61%).

R_F 0.23 (4:1 petrol 40-60 °C/EtOAc + 0.5% AcOH); ν_{max}/cm^{-1} 3100 – 2500 (COO-H), 2938, 2866 (C-H), 1719 (C=O of CO_2H), 1693, 1651 (C=O) 1616, 1593 (C-C Ar); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.11 – 8.04 (2H, m, Ar-H), 7.72 – 7.66 (2H, m, Ar-H), 2.64 (2H, t, *J*=7.4 Hz, $CC\underline{H}_2CH_2$), 2.37 (2H, t, *J*=7.4 Hz, $CC\underline{H}_2CH_2$), 2.19 (3H, s, CH_3), 1.70 (2H, p, *J*=7.5 Hz, $CH_2C\underline{H}_2CH_2$), 1.55 – 1.42 (4H, m, alkyl CHs); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.5 (C), 184.8 (C), 178.4 (C), 147.3 (C), 143.4 (C), 133.49 (CH), 133.46 (CH), 132.4 (C), 126.5 (CH), 126.4 (CH), 33.8 (CH_2), 29.5 (CH_2), 28.4 (CH_2), 27.0 (CH_2), 24.6 (CH_2), 12.8 (CH_3) (one overlapping peak); NMR data matches literature values;[187] m.p. = 102 °C (lit.[187] 103-105 °C).

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Appendix – List of Publications

Chirality Transfer in Gold(I)-Catalysed Hydroalkoxylation of 1,3-Disubstituted Allenes

S. Webster, D. R. Sutherland and A.-L. Lee, *Chem. -Eur. J.*, 2016, **22**, 18593-18600 (Hot Paper)

Gold(I)-Catalysed Hydroarylation of 1,3-Disubstituted Allenes with Efficient Axial-to-Point Chirality Transfer

D. R. Sutherland, L. Kinsman, S. M. Angiolini, G. M. Rosair and A.-L. Lee, *Chem. -Eur. J.*, 2018, **24**, 7002-7009 (VIP Paper)

Dual Gold and Photoredox Catalysed C–H Activation of Arenes for Aryl–Aryl Cross Couplings

V. Gauchot, D. R. Sutherland and A. -L. Lee, *Chem. Sci.*, 2017, **8**, 2885-2889

Metal, Photocatalyst and Light-Free, Late-Stage C-H Alkylation of Heteroarenes and 1,4-Quinones Using Carboxylic Acids

D. R. Sutherland, M. Veguillas, C. L. Oates, and A. -L. Lee, *Org. Lett.* 2018, **20**, 6863-6867